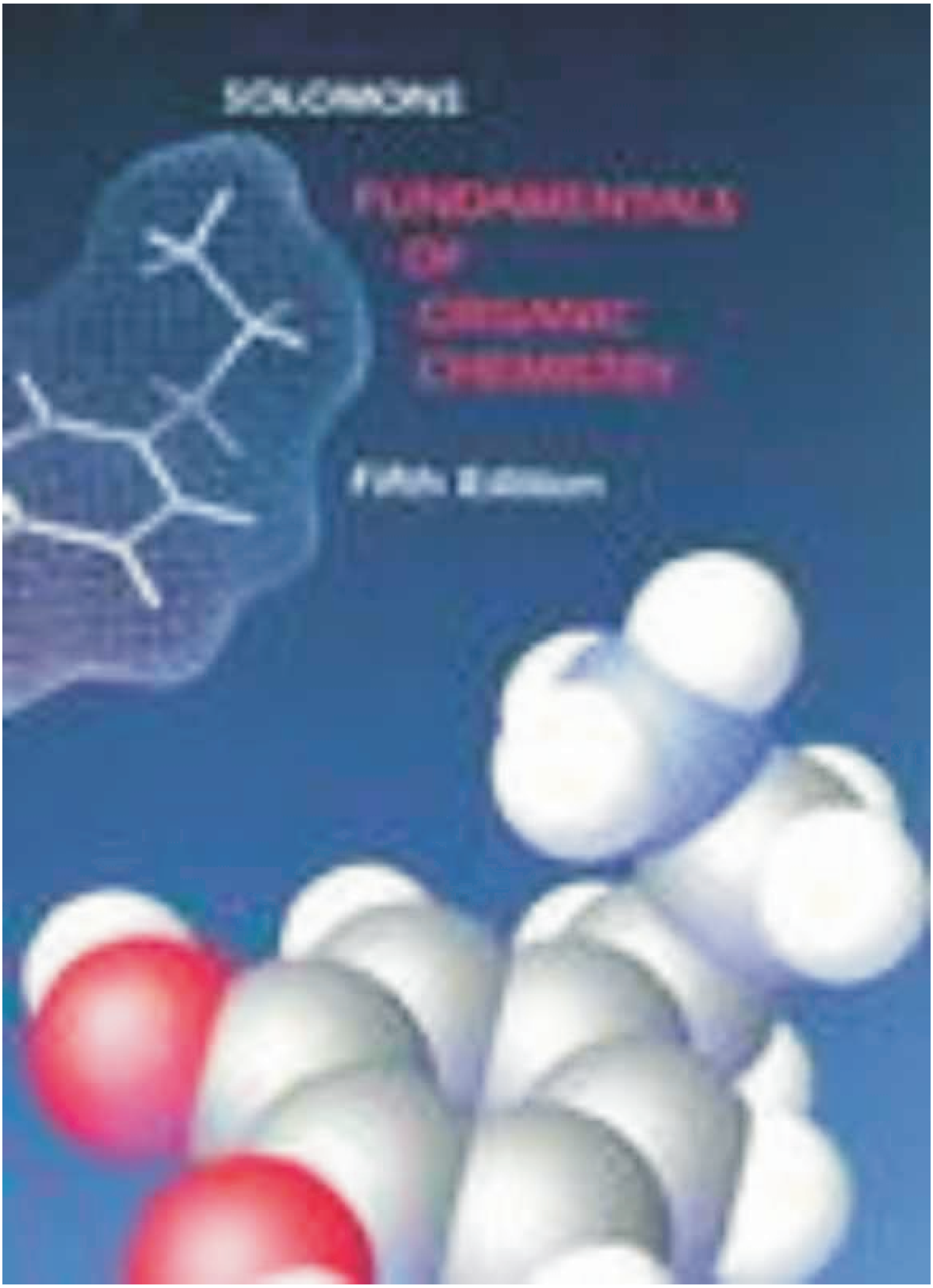
SOLOMONS
FUNDAMENTALS
OF
ORGANIC
CHEMISTRY
Fifth Edition

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ADVICES FOR STUDYING ORGANIC CHEMISTRY

1. **Keep up with your studying day to day — never let yourself get behind, or better yet, be a little ahead of your instructor.** Organic chemistry is a course in which one idea almost always builds on another that has gone before.

2. **Study materials in small units, and be sure that you understand each new section before you go on to the next.** Because of the cumulative nature of organic chemistry, your studying will be much more effective if you take each new idea as it comes and try to understand it completely before you move onto the nest concept.

3. **Work all of the in-chapter and assigned problems.**

4. **Write when you study.** Write the reactions, mechanisms, structures, and so on, over and over again. **You need to know the material so thoroughly that you can explain it to someone else. This level of understanding comes to most of us** (those of us without photographic memories) **through writing.** Only by writing the reaction mechanisms do we pay sufficient attention to their details:

   1) which atoms are connected to which atoms.
   2) which bonds break in a reaction and which bonds form.
   3) the three-dimensional aspects of the structure.

5. **Learning by teaching and explaining (教學相長).** Study with your student peers and practice explaining concepts and mechanisms to each other.

6. **Use the answers to the problems in the *Study Guide* in the proper way:**

   1) Use the *Study Guide* to check your answer after you have finished a problem.
   2) Use the *Study Guide* for a clue when you are completely stuck.

   The value of a problem is in solving it!

7. **Use the introductory material in the *Study Guide* entitled "Solving the puzzle — or — Structure is everything (Almost)"** as a **bridge** from general chemistry to your beginning study of organic chemistry. Once you have **a firm understanding of structure**, the puzzle of organic chemistry can become one of very manageable size and comprehensible pieces.

8. **Use molecular models when you study.**

ADVICES FROM STUDENTS TAKING ORGANIC CHEMISTRY COURSE *CHEM 220A* AT YALE UNIVERSITY

The students listed below from the 2000 fall term have agreed to serve as mentors for *Chem 220a* during the 2001 fall term. They are a superb group of people who did exceptionally well in *Chem 220a* last year. They know the material and how best to approach learning it. Some of them have provided their thoughts on attaining success in the course.

Partial List as of April 20, 2001

- **Catherine Bradford**

My advice on Organic Chemistry:

1. Figure out what works for you and stick with it.
2. **Tests:** I think the key to doing well on the tests is as much about getting a lot of sleep as it is about studying. **It's important to be sharp when you walk into a test,** so that you'll be able to think clearly about the tricky problems. As far as studying goes, **start studying for them a few nights early**. My suggestion for a test on

Friday is to go through the material on Monday, Tuesday, and Wednesday nights, then relax on Thursday night and review as needed.

3. **Problem Sets:** Don't save them for Sunday night. Work out the problem sets so that YOU understand them. Get people's help when needed, but **the most important thing is actually understanding how to get the right answer**.
4. Don't look at Organic Chemistry as if it were a monster to be battled. Rather, think about it as a **challenge**. When you come across a problem that looks long and complicated, just **start writing down what you know and work from there**. You might not get it completely right, but at least you have something.

- **Claire Brickell**

1. As far as I'm concerned, the only way to do well in orgo is to do your work all along. I wish there were a less obnoxious way to say it, but there it is. You probably already think I'm a dork by now, so I'm going to go ahead and say this, too: I like orgo. **There is a really beautiful pattern to it, and once you get past the initial panic you'll realize that most of what you're learning is actually interesting.**
2. The thing is, if you do your work regularly, you'll realize that there really isn't ALL that much of it, and that **it really isn't as hard as you think**. I can't really give you advice on HOW to do your work, because everybody learns differently. I hate memorizing, and I am proud to say that I have never used a flash card in my life. I found ***the best way to learn the reactions was to do as many problems as possible***. Once you've used your knowledge a couple of times, it sort of memorizes itself.
3. Last thing: there are a ton of people out there who know a lot about orgo, and a lot about explaining orgo to other people. Use them. The STARS help sessions are really helpful, as are the tutors.

- **Caroline Drewes**

So I'm sure by now all of you have heard the “nightmares” that organic chemistry is universally associated with. But don't worry!! **The rumored nights of endless memorization and the “impossible” tests that follow them are completely optional.**

By optional I mean that if you put the work in (some time before the night before a test) ***by reading the textbook before class***, ***taking notes*** in Ziegler's (helpful) lectures, ***spending time working through the problem sets*** and going to your invaluable TA's at section, then you'll probably **find orgo to be a challenging class but not unreasonably** so. And don't let yourself be discouraged! Orgo can be frustrating at times (especially at late hours) and you may find yourself swearing off the subject forever, but stick with it! Soon enough you'll be fluent in the whole "***orgo language***" and you'll be able to use the tools you have accumulated to solve virtually any problem — **not necessarily relying on memorization but rather step-by-step learning**. I would swear by **flashcards**, complete with mechanisms, because they're lighter to lug around than the textbook meaning you can keep them in your bag and review orgo when you get a free minute at the library or wherever. Going over the reactions a whole bunch of times well before the test takes 5-10 minutes and will help to solidify the information in your head, saving you from any "day-before-anxiety". One more hint would be to utilize the extensive website — you never know when one of those online ORGO problems will pop up on a test! So good luck and have fun!!

- **Margo Fonder**

I came to the first orgo class of the year expecting the worst, having heard over and over that it would be impossible. But **by mid-semester, the class I'd expected to be a chore had become my favorite**. I think that the key to a positive experience is to ***stay on top of things*** — with this class especially, it's hard to play catch-up. And once you get the hang of it, solving problems can even be fun, because each one is like a little puzzle. **True — the problem sets are sometimes long and difficult, but it's worth it to take the time to work through them because they really do get you to learn the stuff.** Professor Ziegler makes a lot of resources available (especially the old exams, old problem sets, and study aids he has on his website) that are really helpful while studying for exams. I also found copying over my (really messy) class notes to be a good way to study, because I could make sure that I understood everything presented in class at my own pace. My number one piece of advice would probably be to use Professor Ziegler's

office hours! It helped me so much to go in there and work through my questions with him. (Plus, there are often other students there asking really good questions, too.)

- **Vivek Garg**

There's no doubt about it, organic chemistry deals with a LOT of material. How do you handle it and do well? You've heard or will hear enough about going to every class, reading the chapters on time, doing all of the practice problems, making flashcards, and every other possible study technique. Common sense tells you to do all of that anyway, but let's face it, it's almost impossible to do all the time. So, my advice is a bit broader. You've got to know the material AND be able to apply it to situations that aren't cookie-cutter from the textbook or lecture. We'll assume that you can manage learning all of the facts/theories. That's not enough: the difference between getting the average on an orgo test and doing better is applying all of those facts and theories at 9:30 Friday morning. When you study, **don't just memorize reactions** (A becomes B when you add some acid, Y reacts with water to give Z), **THINK about what those reactions let you do**. Can you plot a path from A to Z now? You better, because you'll have to do it on the test. **Also, it's easy to panic in a test.** **DON'T leave anything blank, even if it seems totally foreign to you.** **Use the fundamentals you know, and take a stab at it.** **Partial credit will make the difference.** For me, ***doing the problem sets on my own helped enormously***. Sure, it's faster to work with a group, but forcing yourself to work problems out alone really solidifies your knowledge. The problem sets aren't worth a lot, and **it's more important to think about the concepts behind each question than to get them right**. Also, the Wade textbook is the best science text I've ever had. Tests are based on material beyond just lecture, so make the text your primary source for the basics. Lastly, you're almost certainly reading this in September, wondering what we mean by writing out mechanisms and memorizing reactions...come back and **re-read all of this advice after the first test or two**, and it will make much more sense. Good luck!

- **Lauren Gold**

Everyone hears about elusive organic chemistry years before arriving at college, primarily as the bane of existence of premeds and science majors. The actual experience however, as my classmates and I quickly learned, is not painful or impossible but rather challenging, rewarding, and at times, even fun. All that's required, moreover, is **an open mind and a willingness to study the material until it makes sense**. No one will deny that **orgo is a LOT of work**, but by coming to class, reading the chapters, starting problem sets early and most of all, working in study groups it all becomes pretty manageable. By forming a good base in the subject it becomes easier and more interesting as you go along. Moreover, the relationships you'll make with other orgo'ers walking up science hill at 9 am are definitely worth it.

- **Tomas Hooven**

When you take the exams, you'll have to be very comfortable WRITING answers to organic problems quickly. This may be self-evident, but I think ***many students spend a lot of time LOOKING at their notes or the book while they study without writing anything***. I don't think reading about chemical reactions is anywhere near as useful as drawing them out by hand. I structured my study regime so that I wrote constantly. **First, I recopied my lecture notes to make them as clear as possible.** **Then I made flash cards to cover almost every detail of the lectures.** After memorizing these cards, **I made a chart of the reactions and mechanisms that had been covered and memorized it.** Also, throughout this process **I worked on relevant problems from the book to reinforce the notes and reactions** I was recopying and memorizing.

- **Michael Kornberg**

Most of the statements you've read so far on this page have probably started out by saying that Organic Chemistry really isn't that bad and can, in fact, be pretty interesting. I think it's important to understand from the start that this is completely true…I can almost assure you that you will enjoy Orgo much more than General Chemistry, and the work & endash; although there may be a lot of it & endash; is certainly not overwhelming. Just **stay on top of it** and you'll be fine. **Always read the chapter before starting the**

problem set, and make sure that you read it pretty carefully, doing some of the practice problems that are placed throughout the chapter to make sure that you really understand the material. Also, **spend a lot of time on the problem sets** & endash; this will really help you to solidify your understanding and will pay off on the exams.

As for the exams, everyone knows how they study best. Just be sure to **leave yourself enough time to study** and always go over the previous years' exams that Dr. Ziegler posts on the website & endash; they're a really good indicator of what's going to be on your exam. That's all I have to say, so good luck.

- **Kristin Lucy**

The most important concept to understand about organic chemistry is that it is a “do-able” subject. Orgo's impossible reputation is not deserved; however, **it is a subject that takes a lot of hard work** along the way. As far as tips go, **read the chapters before the lectures**; **concepts will make a lot more sense**. **Set time aside to do the problem sets**; they do tend to take a while the first time around. Make use of the problems in the book (I did them while I read through the chapter) and the study guide and set **aside several days prior to exams for review**. Your TA can be a secret weapon — they have all the answers! Also, everything builds on everything else continuing into 2nd semester. Good luck and have fun with the chairs and boats!

- **Sean McBride**

Organic chemistry can, without a doubt, be an intimidating subject. You've heard the horror stories from the now ex-premeds about how orgo single handedly dashed their hopes of medical stardom (centering around some sort of ER based fantasy). But do not fret! Orgo is manageable. ***Be confident in yourself.*** You can handle this. With that said, the practical advise I can offer is twofold:

1. When studying for the tests, look over the old problem sets, do the problems from the back of the book, and utilize the website!! **Time management is crucial. Break down the studying. Do not cram.** Orgo tests are on Fridays. It helps if you divide the material and study it over the course of the week.

2. **Work in a group when doing the problem sets.** **Try to work out the problems on your own first**, then meet together and go over the answers. I worked with the same group of 4 guys for the entire year and it definitely expedited the problem set process. Not only that, but it also allows you to realize your mistakes and to help explain concepts to others; ***the best way to learn material is to attempt to teach it***. It may feel overwhelming at times and on occasion you may sit in lecture and realize you have no idea what is going on. That is completely and totally normal.

- **Timothy Mosca**

So you're about to undertake one of the greatest challenges of academia. Yes, young squire, welcome to Organic Chemistry. Let's dispel a myth first: **IT'S NOT IMPOSSIBLE!** I won't lie & it is a challenge and it's gonna take some heavy work, but in the end, contrary to the naysayers, it's worth it. **Orgo should be taken a little at a time** and if you remember that, you're fine. Never try to do large amounts of Orgo in small amounts of time. Do it gradually, a little every day. The single most important piece of advice I can give is to **not fall behind**. You are your own worst enemy if you get behind in the material. If you **read BEFORE the lectures**, **they're going to make a whole lot more sense and it'll save you time**, come exams, so you're not struggling to learn things anew two days before the test, rather, you're reviewing them. It'll also save you time and worry on the problem sets. Though they can be long and difficult, and you may wonder where in Sam Hill some of the **questions** came from, **they are a GREAT way to practice what you've learned and reinforce what you know**. And (hint hint!), **the problem sets are fodder for exams**; similar problems MAY appear! Also, use your references: if there's something you don't get, don't let it fester, talk to the mentors, talk to your TA, visit Professor Ziegler and don't stop until you get it! Never adopt the attitude that a certain concept is needed for 1 exam. See, ***Orgo has this dastardly way of building on itself and stuff from early on reappears EVERYWHERE!*** You'll save yourself time if, **every now and again, you review**. **Make a big ol' list of reactions and mechanisms somewhere and keep going back to it**. Guaranteed, it will help! And finally, don't get discouraged by minor setbacks & even *Wade* (the author of the text)

got a D on his second exam and so did this mentor!! Never forget & Orgo can be fun! Yes, really, it can be; I'm not just saying that. Like any good thing, it requires practice in problems, reactions, thinking, and, oh yeah, problems. But by the end, it actually gets easy! So, BEST OF LUCK!!!!

- **Raju Patel**

If you are reading these statements of advise, you already have the most valuable thing you'll need to do well in organic chemistry: **a desire to succeed**. I felt intimidated by the mystique that seems to surround this course, about how painful and difficult it is, but realized it doesn't need to be so. **If you put in the time**, and I hesitate to say hard work because it can really be enjoyable, **you will do well**. It's in the approach: think of it as a puzzle that you need to solve and to do so you acquire the tools from examples you see in the book and the reasoning Prof. Ziegler provides in lecture. Take advantage of all resources to train yourself like your TA and the website. Most importantly, **do mad amounts of practice problems** (make the money you invested in the solutions manual and model kit worth it). When the time comes to take the test, you won't come up against anything you can't handle. Once patterns start emerging for you and you realize that **all the information that you need is right there in the problem**, that it is just a matter of finding it, it will start feeling like a game. So play hard.

- **Sohil Patel**

Chemistry 220 is a very interesting and manageable course. The course load is certainly substantial but can be handled by keeping up with the readings and using the available online resources consistently through the semester. ***It always seemed most helpful to have read the chapters covered in lecture before the lecture was given so that the lecture provided clarification and reinforcement of the material you have once read.*** **Problem sets provided a valuable opportunity to practice and apply material you have learned in the readings and in lecture.** In studying for tests, **a certain degree of memorization is definitely involved**, but **by studying mechanisms and understanding the chemistry behind the various reactions, a lot of unnecessary memorization is**

avoided. Available problem sets and tests from the past two years were the most important studying tools for preparing for tests because they ingrain the material in your head, but more importantly, they help you think about the chemistry in ways that are very useful when taking the midterms and final exam. And more than anything, **organic chemistry certainly has wide applications that keep the material very interesting**.

- **Eric Schneider**

I didn't know what to expect when I walked into my first ORGO test last year. To put it plainly, I didn't know how to prepare for an ORGO test — my results showed. The first ORGO test was a wake-up call for me, but it doesn't need to be for you. My advice about ORGO is to **make goals for yourself and set a time-frame for studying**. Lay out clear objectives for yourself and use all of the resources available (if you don't you're putting yourself at a disadvantage). Professor Ziegler posts all of the old exams and problem sets on the Internet. They are extremely helpful. Reading the textbook is only of finite help — ***I found that actually doing the problems is as important or even more important than reading the book because it solidifies your understanding***. That having been said, **don't expect ORGO to come easily** — it is almost like another language. **It takes time to learn, so make sure that you give yourself enough time.** But once you have the vocabulary, it's not that bad. While knowing the mechanisms is obviously important, you need to understand the concepts behind the mechanisms to be able to apply them to exam situation. Remember — ORGO is like any other class in the sense that the more you put in, the more you get out. It is manageable. Just one more tip — **go to class!**

- **Stanley Sedore**

1. Welcome to Organic Chemistry. The first and most important thing for success in this class is to **forget everything you have ever heard about the "dreaded" orgo class**. It is a different experience for everyone, and **it is essential that you start the class with a positive and open mind**. It is not like the chemistry you have had in the past and you need to give it a chance as its own class before you judge it and your

own abilities.

2. Second, organic chemistry is about organization. You'll hear the teachers say it as well as the texts: organic chemistry is NOT about memorization. **There are hundreds of reactions which have already been organized by different functional groups. If you learn the chemistry behind the reactions and when and why they take place**, **you'll soon see yourself being able to apply these reactions without memorization**.
3. Third, **practice**. This is something new, and **like all things, it takes a lot of practice to become proficient at it**. Do the problems as you read the chapters, do the problems at the end of the chapters, and if you still feel a bit uneasy, ask the professor for more.
4. Remember, many people have gone through what you are about to embark upon and done fine. **You can and will do fine**, and there are many people who are there to help you along the way

- **Hsien-yeang Seow**

Organic Chemistry at Yale has an aura of being impossible and "***the most difficult class at Yale***". It is certainly a challenging class but is in no way impossible. Do not be intimidated by what others say about the class. **Make sure that you do the textbook readings well before the tests — I even made my own notes on the chapters.** The textbook summarizes the mechanisms and reactions very well. Class helps to re-enforce the textbook. Moreover, the textbook problems are especially helpful at the beginning of the course. ***DO NOT fall behind...make sure you stay on top of things right at the beginning***. **Organic Chemistry keeps building on the material that you have already learned.** I assure you, that if you keep up, the course will seem easier and easier. I personally feel that the mechanisms and reactions are the crux of the course. I used a combination of flashcards and in-text problems to help memorize reactions. However, as the course went on, I quickly found that instead of memorizing, I was **actually learning and understanding the mechanisms and from there it was much easier to grasp the concepts and apply them to any problem**. There are lots of

resources that are designed to HELP you...The TA's are amazing, the old problems sets and tests were very helpful for practicing before test, and the solutions manual is a good idea. Good luck.

- **Scott Thompson**

The **best way** to do well in Organic Chemistry is to really try to **understand the underlying concepts of how and why things react the way that they do**. **It is much easier to remember a reaction or mechanism if you have a good understanding of why it is happening.** Having a good grasp of the concepts becomes increasingly beneficial as the course progresses. So, I recommend working hard to understand everything at the **BEGINNING** of the semester. It will pay off in the exams, including those in the second semester. **If you understand the concepts well, you will be able to predict how something reacts even if you have never seen it before.**

Organic Chemistry is just like any other course; the more time you spend studying, the better you will do.

1. **Read the assigned chapters thoroughly and review the example problems.**
2. **Work hard on the problem sets, they will be very good preparation.**
3. **Do not skip lectures.**

Most importantly, **begin your study of "Orgo" with an open mind**. Once you get past all the hype, you'll see that it's a cool class and you'll learn some really interesting stuff. Good Luck!

1. **Keep up with your studying day to day.**
2. **Focus your study.**
3. **Keep good lecture notes.**
4. **Carefully read the topics covered in class.**
5. **Work the problems.**

COMPOUNDS AND CHEMICAL BONDS

1.1 INTRODUCTION

1. Organic chemistry is the study of *the compounds of carbon*.
2. The compounds of carbon are the central substances of which all living things on this planet are made.
   1) DNA: the giant molecules that contain all the genetic information for a given species.
   2) proteins: blood, muscle, and skin.
   3) enzymes: catalyze the reactions that occur in our bodies.
   4) furnish the energy that sustains life.

3. Billion years ago most of the carbon atoms on the earth existed as CH_4:
   1) CH_4, H_2O, NH_3, H_2 were the main components of the primordial atmosphere.
   2) Electrical discharges and other forms of highly energetic radiation caused these simple compounds to fragment into highly reactive pieces which combine into more complex compounds such as amino acids, formaldehyde, hydrogen cyanide, purines, and pyrimidines.
   3) Amino acids reacted with each other to form the first protein.
   4) Formaldehyde reacted with each other to become sugars, and some of these sugars, together with inorganic phosphates, combined with purines and pyrimidines to become simple molecules of ribonucleic acids (RNAs) and DNA.

4. We live in an *Age of Organic Chemistry*:
   1) clothing: natural or synthetic substance.
   2) household items:
   3) automobiles:
   4) medicines:
   5) pesticides:

5. Pollutions:
   1) insecticides: natural or synthetic substance.
   2) PCBs:

3) dioxins:

4) CFCs:

1.2 THE DEVELOPMENT OF ORGANIC CHEMISTRY AS A SCIENCE

1. The ancient Egyptians used indigo (藍靛) and alizarin (茜素) to dye cloth.
2. The Phoenicians (腓尼基人) used the famous “royal purple (深藍紫色)”, obtained from mollusks (墨魚、章魚、貝殼等軟體動物), as a dyestuff.
3. As a science, organic chemistry is less than 200 years old.

1.2A Vitalism

“Organic” —— derived from living ***organism*** (In 1770, Torbern Bergman, Swedish chemist)

⇒ the study of compounds extracted from living organisms

⇒ such compounds needed **“vital force”** to create them

1. In 1828, Friedrich Wöhler Discovered:

Ammonium cyanate (***inorganic***) → Urea (***organic***)

1.2B Empirical and Molecular Formulas

1. In 1784 Antoine Lavoisier (法國化學家拉瓦錫) first showed that organic compounds were composed primarily of carbon, hydrogen, and oxygen.
2. Between 1811 and 1831, *quantitative* methods for determining the composition of

organic compounds were developed by Justus Liebig (德國化學家), J. J. Berzelius, J. B. A. Dumas (法國化學家).

3. In 1860 Stanislao Cannizzaro (義大利化學家坎尼薩羅) showed that the earlier hypothesis of Amedeo Avogadro (1811, 義大利化學家及物理學家亞佛加厥) could be used to distinguish between **empirical** and **molecular formulas**.

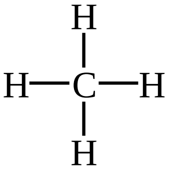
molecular formulas C_2H_4 (ethylene), C_5H_{10} (cyclopentane), and C_6H_{12} (cyclohexane) all have the same empirical formula CH_2.

1.3 THE STRUCTURAL THEORY OF ORGANIC CHEMISTRY

1.3A. The Structural Theory: (1858 ~ 1861)

August Kekulé (German), Archibald Scott Couper (Briton), and Alexander M. Butlerov

1. The atoms can form a fixed number of bonds (**valence**):



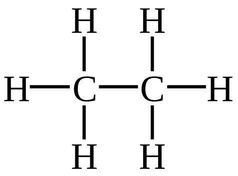
Carbon atoms are tetravalent

Oxygen atoms are divalent

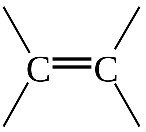
Hydrogen and halogen atoms are monovalent

2. A carbon atom can use one or more of its valence to form bonds to other atoms:

Carbon-carbon bonds



Single bond



Double bond

Triple bond

3. Organic chemistry: **A study of the compounds of carbon** (Kekulé, 1861).

1.3B. Isomers: The Importance of Structural Formulas

1. **Isomers**: **different compounds that have the same molecular formula**
2. There are two isomeric compounds with molecular formula C_2H_6O:
   1) dimethyl ether: a gas at room temperature, does not react with sodium.
   2) ethyl alcohol: a liquid at room temperature, does react with sodium.

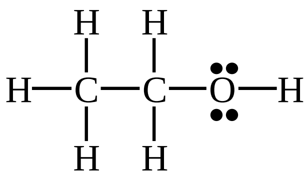
Table 1.1 Properties of ethyl alcohol and dimethyl ether

	Ethyl Alcohol C_2H_6O	Dimethyl Ether C_2H_6O
Boiling point, °C[a]	78.5	–24.9
Melting point, °C	–117.3	–138
Reaction with sodium	Displaces hydrogen	No reaction

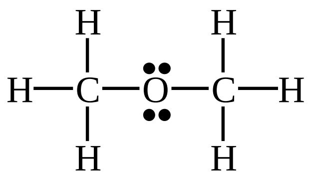
[a] Unless otherwise stated all temperatures in this text are given in degree Celsius.

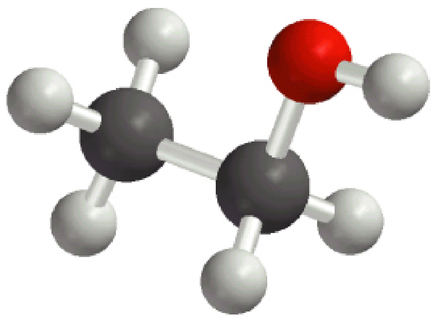
3. The two compounds differ in their **connectivity**: C–O–C and C–C–O

Ethyl alcohol

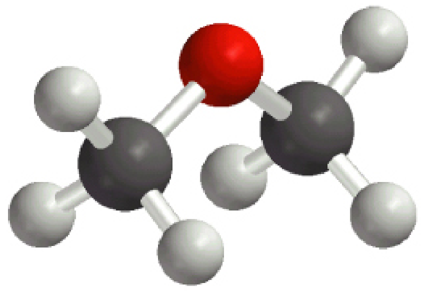


Dimethyl ether





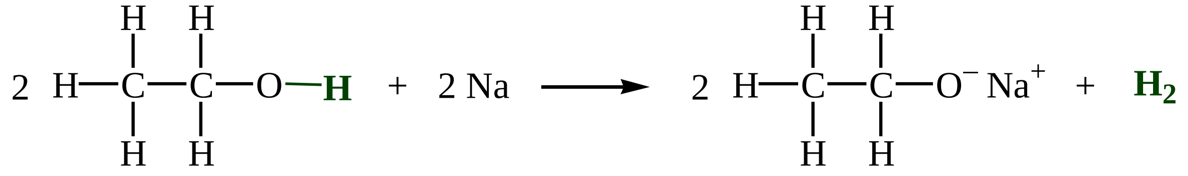
Ethyl alcohol



Dimethyl ether

Figure 1.1 Ball-and-stick models and structural formulas for ethyl alcohol and dimethyl ether

1) O–**H**: accounts for the fact that ethyl alcohol is a liquid at room temperature.



$$2\ H{-}O{-}\mathbf{H} + 2\ Na \longrightarrow 2\ H{-}O^{-}\ Na^{+} + \mathbf{H_2}$$

2) C–**H**: normally unreactive

4. **Constitutional isomers:* different compounds that have the same molecular formula, but differ in their connectivity** (the sequence in which their atoms are bounded together).

* An older term, **structural isomers**, is recommended by the International Union of Pure and Applied Chemistry (IUPAC) to be abandoned.

1.3C. The Tetrahedral Shape of Methane

1. In 1874, Jacobus H. van't Hoff (Netherlander) & Joseph A. Le Bel (French):
   The four bonds of the carbon atom in methane point toward the corners of a regular tetrahedron, the carbon atom being placed at its center.

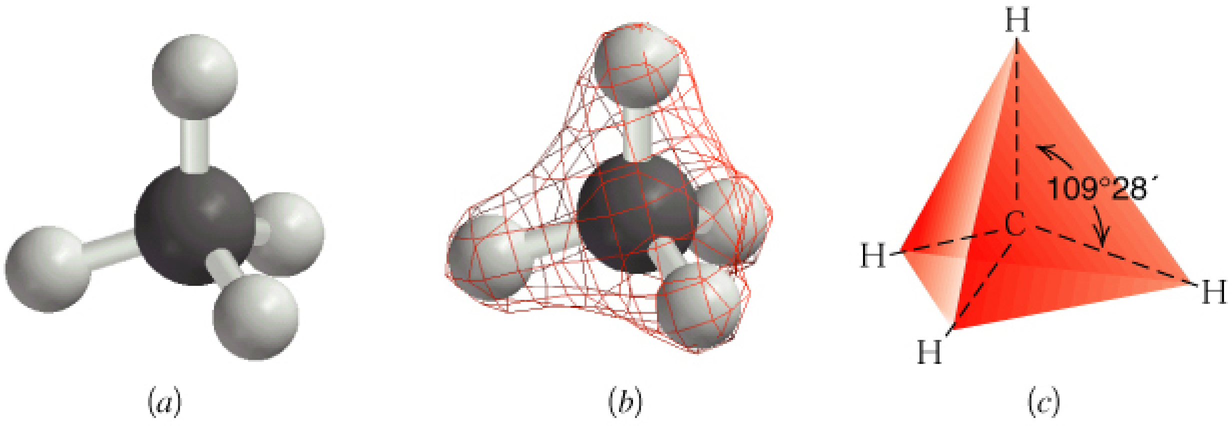


Figure 1.2 The tetrahedral structure of methane. Bonding electrons in methane principally occupy the space within the wire mesh.

1.4 Chemical Bonds: The Octet Rule

Why do atoms bond together? more stable (has less energy)

How to describe bonding?

1. G. N. Lewis (of the University of California, Berkeley; 1875~1946) and Walter Kössel (of the University of Munich; 1888~1956) proposed in 1916:
   1) The **ionic** (or **electrovalent**) bond: formed by the transfer of one or more electrons from one atom to another to create ions.
   2) The **covalent** bond: results when atoms share electrons.
2. Atoms without the electronic configuration of a noble gas generally react to produce such a configuration.

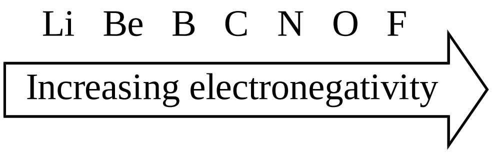
1.4A Ionic Bonds

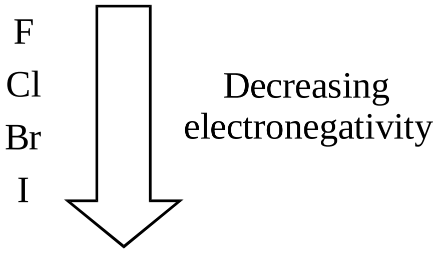
1. **Electronegativity measures the ability of an atom to attract electrons.**

Table 1.2 Electronegativities of Some of Elements

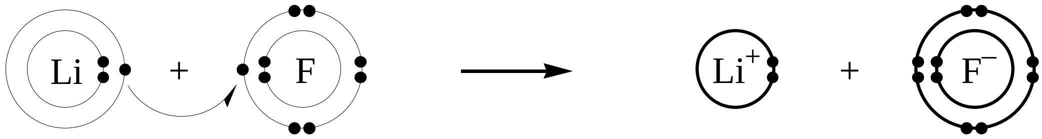
H 2.1						
Li 1.0	**Be** 1.5	**B** 2.0	**C** 2.5	**N** 3.0	**O** 3.5	**F** 4.0
Na 0.9	**Mg** 1.2	**Al** 1.5	**Si** 1.8	**P** 2.1	**S** 2.5	**Cl** 3.0
K 0.8						**Br** 2.8

   1) The electronegativity increases across a horizontal row of the periodic table from left to right:
   2) The electronegativity decreases go down a vertical column:





3) 1916, Walter Kössel (of the University of Munich; 1888~1956)



electron transfer　　He configuration　　Ne configuration　　ionic bond

4) Ionic substances, because of their strong internal electrostatic forces, are usually very high melting solids, often having melting points above 1,000 °C.

5) In polar solvents, such as water, the ions are solvated, and such solutions usually conduct an electric current..

1.4B Covalent Bonds

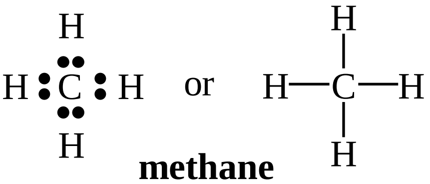
1. **Atoms achieve noble gas configurations by sharing electrons.**

1) Lewis structures:

H_2

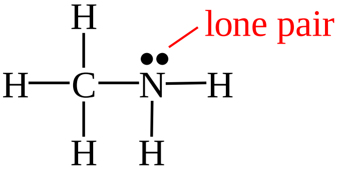
each H shares two electrons (He configuration)

Cl_2

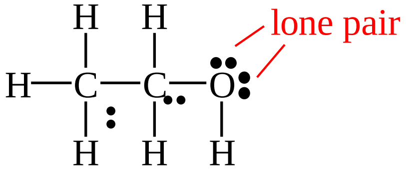


methane

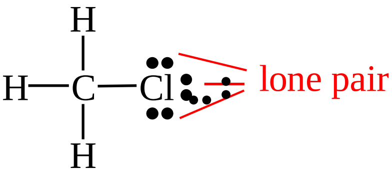
N_2



methyl amime

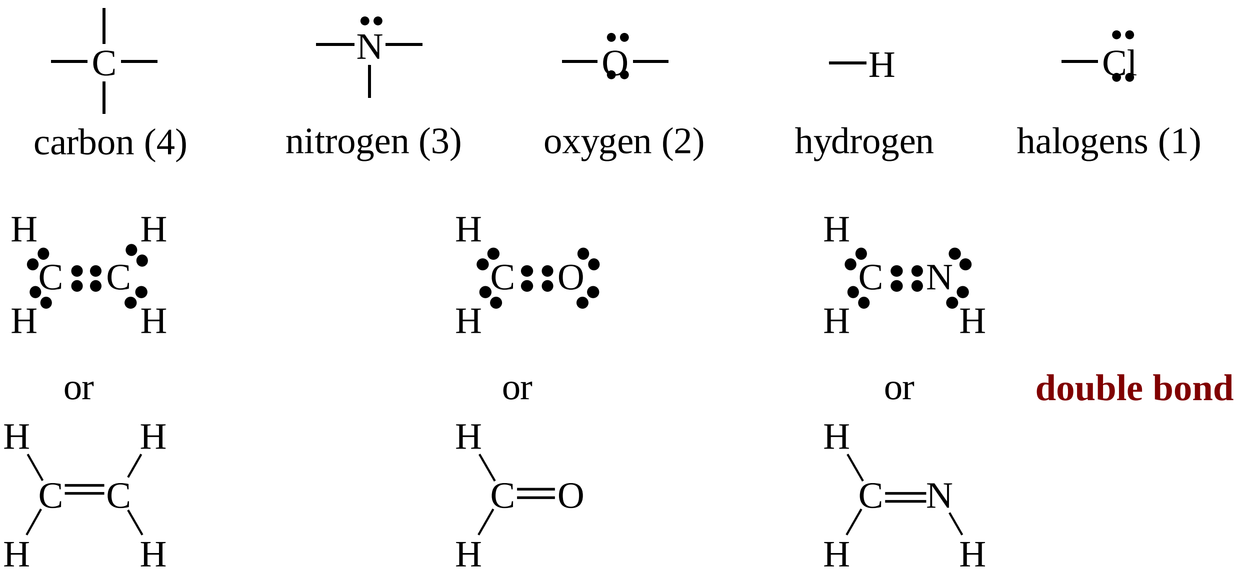


ethanol



chloromethane

: nonbonding electrons ⇒ affect the reactivity of the compound



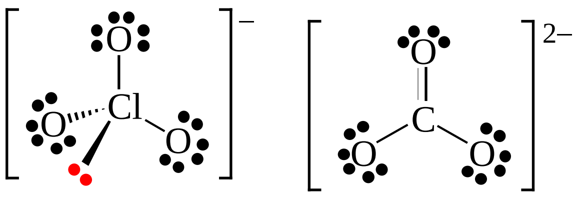
ethylene **formaldehyde** **formaldimine**

1.5 WRITING LEWIS STRUCTURES

1.5A. Lewis structure of CH_3F

1. The number of valence electrons of an atom is equal to the group number of the atom.
2. For an ion, add or subtract electrons to give it the proper charge.
3. Use multiple bonds to give atoms the noble gas configuration.

1.5B. Lewis structure of ClO_3^- and CO_3^{2-}



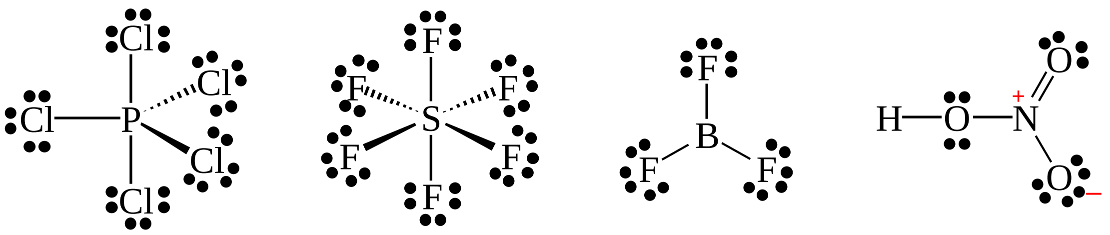
1.6 EXCEPTIONS TO THE OCTET RULE

1.6A. PCl_5

1.6B. SF_6

1.6C. BF_3

1.6D. HNO_3 ($HONO_2$)



1.7 FORMAL CHARGE

1.7A In normal covalent bond:

1. Bonding electrons are shared by both atoms. Each atom still "owns" one electron.
2. "**Formal charge**" is calculated by subtracting the number of valence electrons assigned to an atom in its bonded state from the number of valence electrons it has as a neutral free atom.

1.7B For methane:

1. Carbon atom has four valence electrons.
2. Carbon atom in methane still owns four electrons.
3. Carbon atom in methane is electrically neutral.

1.7C For ammonia:

1. Atomic nitrogen has five valence electrons.
2. Ammonia nitrogen still owns five electrons.
3. Nitrogen atom in ammonia is electrically neutral.

1.7D For nitromethane:

1. Nitrogen atom:
   1) Atomic nitrogen has five valence electrons.
   2) Nitromethane nitrogen has only *four* electrons.
   3) Nitrogen has lost an electron and must have a positive charge.

2. Singly bound oxygen atom:
   1) Atomic oxygen has six valence electrons.
   2) Singly bound oxygen has *seven* electrons.
   3) Singly bound oxygen has gained an e^- and must have a negative charge.

1.7E Summary of Formal Charges

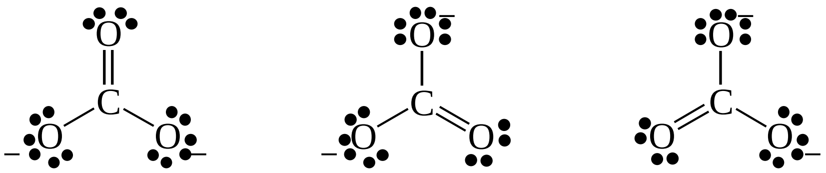
See **Table 1.3**

1.8 RESONANCE

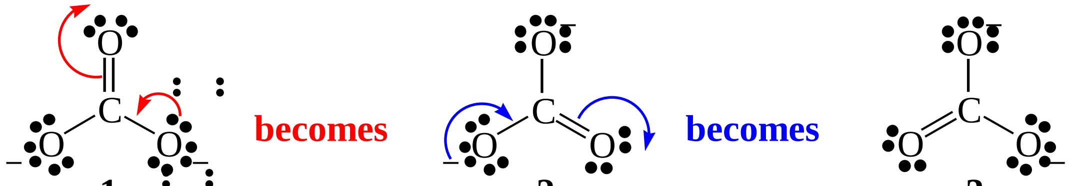
1.8A. General rules for drawing "*realistic*" resonance structures:

1. Must be valid Lewis structures.
2. Nuclei cannot be moved and bond angles must remain the same. Only electrons may be shifted.
3. The number of unpaired electrons must remain the same. All the electrons must remain paired in all the resonance structures.
4. Good contributor has all octets satisfied, as many bonds as possible, as little charge separation as possible. Negative charge on the more EN atoms.
5. Resonance stabilization is most important when it serves to delocalize a charge over two or more atoms.
6. **Equilibrium:** $\rightleftharpoons$
7. **Resonance:** $\longleftrightarrow$

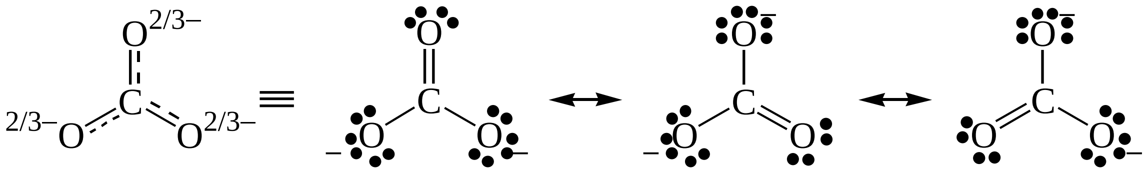
1.8B. CO_3^{2-}



1 **2** **3**



1 **2** **3**



1 **2** **3**

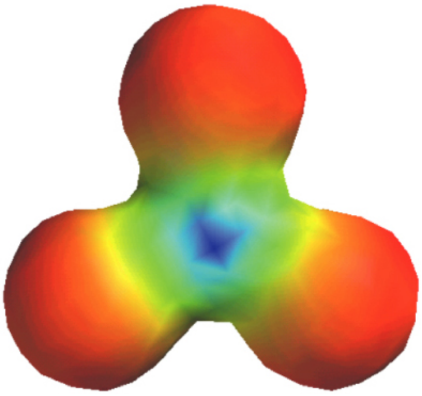


Figure 1.3 A calculated electrostatic potential map for carbonate dianion, showing the equal charge distribution at the three oxygen atoms. In electrostatic potential maps like this one, colors trending toward red mean increasing concentration of negative charge, while those trending toward blue mean less negative (or more positive) charge.

1.9 QUANTUM MECHANICS

1.9A Erwin Schrödinger, Werner Heisenberg, and Paul Dirac (1926)

1. **Wave mechanics** (Schrödinger) or **quantum mechanics** (Heisenberg)

   1) Wave equation ⇒ wave function (solution of wave equation, denoted by Greek

letter psi (Ψ)

2) Each wave function corresponds to a different state for the electron.

3) Corresponds to each state, and calculable from the wave equation for the state, is a particular energy.

4) The value of a wave function: **phase sign**

5) **Reinforce:** a crest meets a crest (waves of the same phase sign meet each other) ⇒ add together ⇒ resulting wave is larger than either individual wave.

6) **Interfere:** a crest meets a trough (waves of opposite phase sign meet each other) ⇒ subtract each other ⇒ resulting wave is smaller than either individual wave.

7) **Node:** the value of wave function is zero ⇒ **the greater the number of nodes, the greater the energy**.

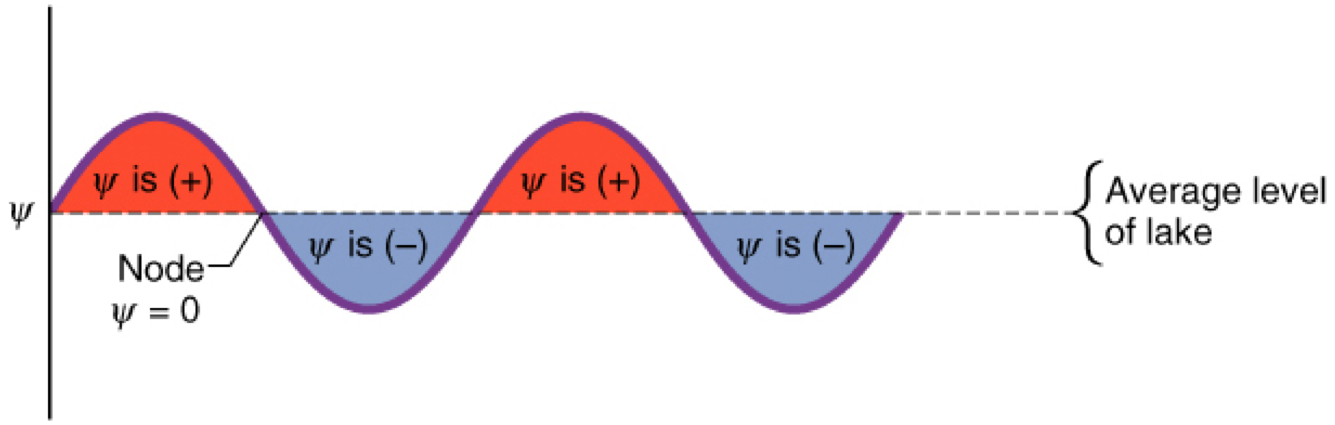


Figure 1.4 A wave moving across a lake is viewed along a slice through the lake. For this wave the wave function, Ψ, is plus (+) in crests and minus (–) in troughs. At the average level of the lake it is zero; these places are called nodes.

1.10 Atomic Orbitals

1.10A. Electron Probability Density:

1. Ψ^2 for a particular location (x,y,z) expresses the **probability** of finding an electron at that particular location in space (Max Born).

1) Ψ^2 is large: large **electron probability density**.

2) **Plots of Ψ^2 in three dimensions generate the shapes of the familiar *s*, *p*, and *d* atomic orbitals.**

3) **An orbital is a region of space where the probability of finding an electron is large** (the volumes would contain the electron 90-95% of the time)**.**

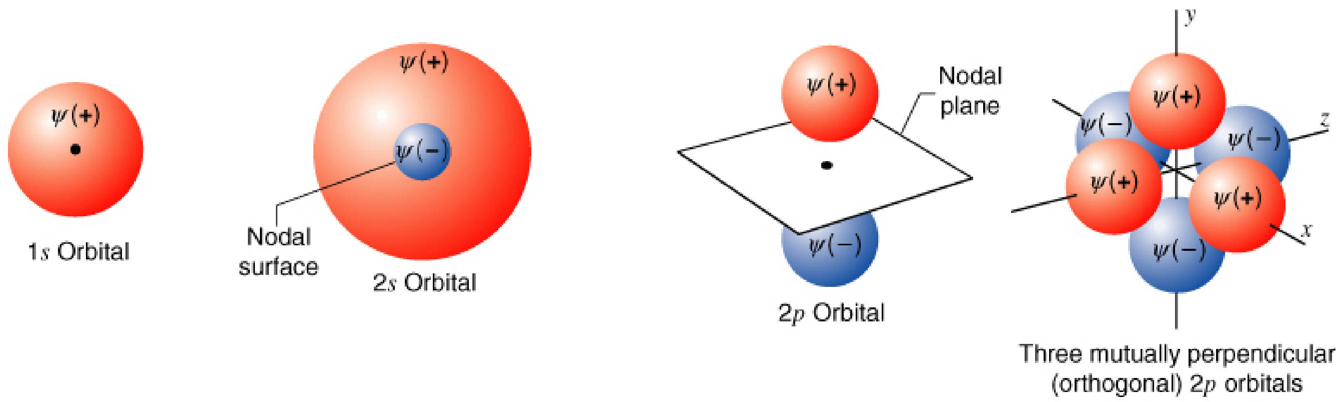


Figure 1.5 The shapes of some s and *p* orbitals. Pure, unhybridized *p* orbitals are almost-touching spheres. The *p* orbitals in hybridized atoms are lobe-shaped (Section 1.14).

1.10B. Electron configuration:

1. **The aufbau principle** (German for "building up")**:**
2. **The Pauli exclusion principle:**
3. **Hund's rule:**

1) Orbitals of equal energy are said to **degenerate orbitals**.

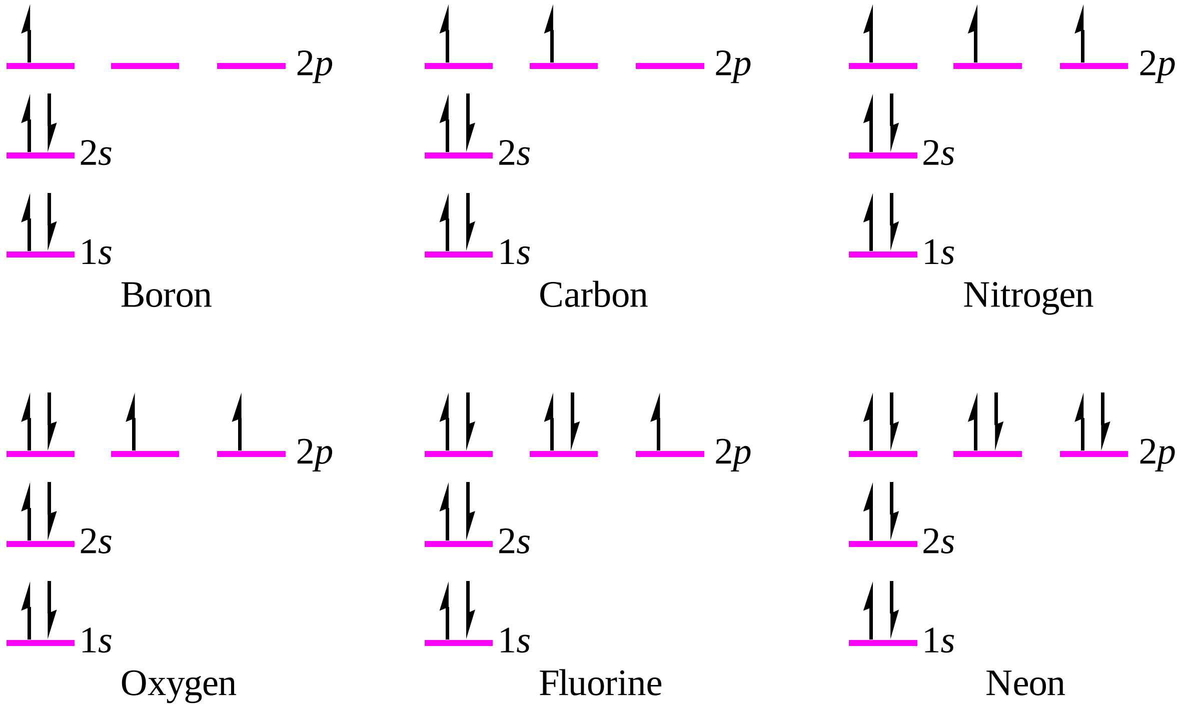


Figure 1.6 The electron configurations of some second-row elements.

1.11 MOLECULAR ORBITALS

1.11A. Potential energy:

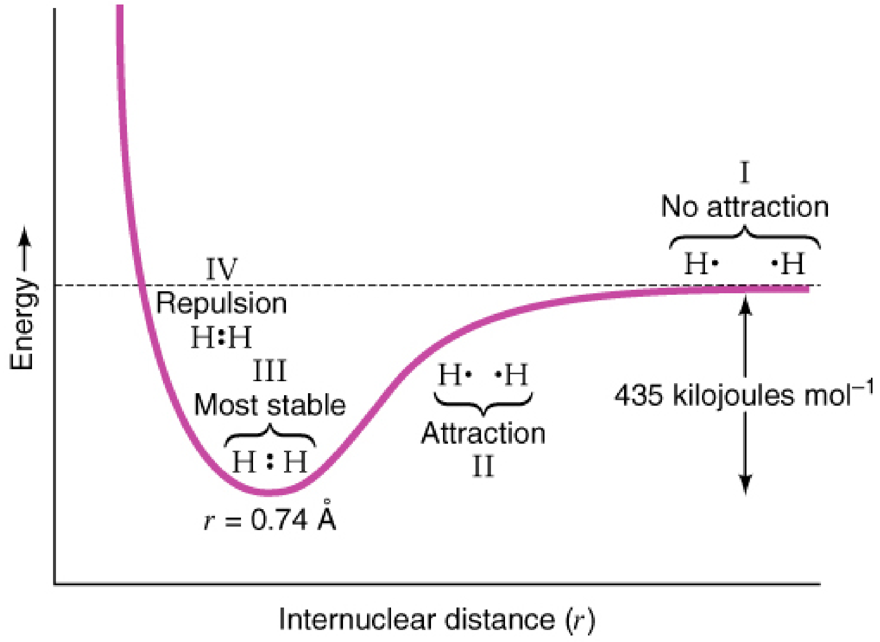


Figure 1.7 The potential energy of the hydrogen molecule as a function of internuclear distance.

1. Region **I**: the atoms are far apart ⇒ **No attraction**
2. Region **II**: each nucleus increasingly attracts the other's electron ⇒ the attraction more than compensates for the repulsive force between the two nuclei (or the two electrons) ⇒ **the attraction lowers the energy of the total system**
3. Region **III**: the two nuclei are 0.74 Å apart ⇒ **bond length** ⇒ **the most stable (lowest energy) state is obtained**
4. Region **IV**: the repulsion of the two nuclei predominates ⇒ **the energy of the system rises**

1.11B. Heisenberg Uncertainty Principle

1. We can not know simultaneously the position and momentum of an electron.
2. We describe the electron in terms of probabilities (Ψ^2) of finding it at particular place.

   1) ***electron probability density*** ⇒ **atomic orbitals (AOs)**

1.11C. Molecular Orbitals

1. **AOs** combine (overlap) to become **molecular orbitals (MOs).**

   1) The **MOs** that are formed encompass both nuclei, and, in them, the electrons can move about both nuclei.
   2) The **MOs** ***may contain a maximum of two spin-paired electrons***.
   3) The number of **MOs** ***that result always equals the number of AOs that combine***.

2. **Bonding molecular orbital (Ψ_{molec}):**

   1) **AOs *of the same phase sign overlap*** ⇒ **leads to *reinforcement* of the wave function** ⇒ **the value of is larger between the two nuclei** ⇒ **contains both electrons in the lowest energy state, ground state**

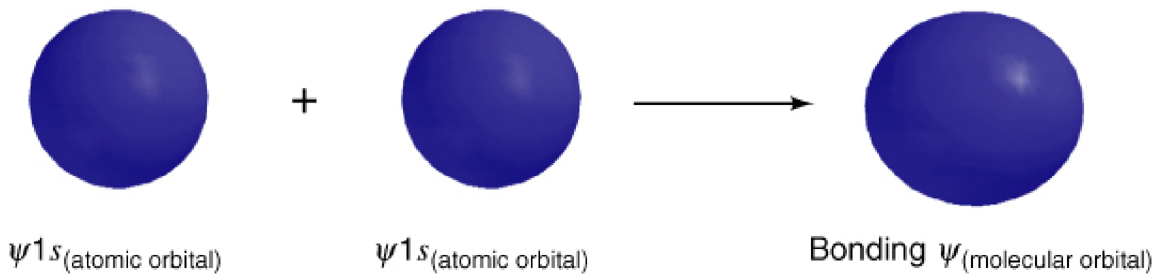


Figure 1.8 The overlapping of two hydrogen 1s atomic orbitals with the same phase sign (indicated by their identical color) to form a bonding molecular orbital.

3. **Antibonding molecular orbital (ψ^*_{molec}):**

 1) ***AOs of opposite phase sign overlap* ⇒ leads to *interference* of the wave function in the region between the two nuclei ⇒ a node is produced ⇒ the value of is smaller between the two nuclei ⇒ the highest energy state, excited state ⇒ contains no electrons**

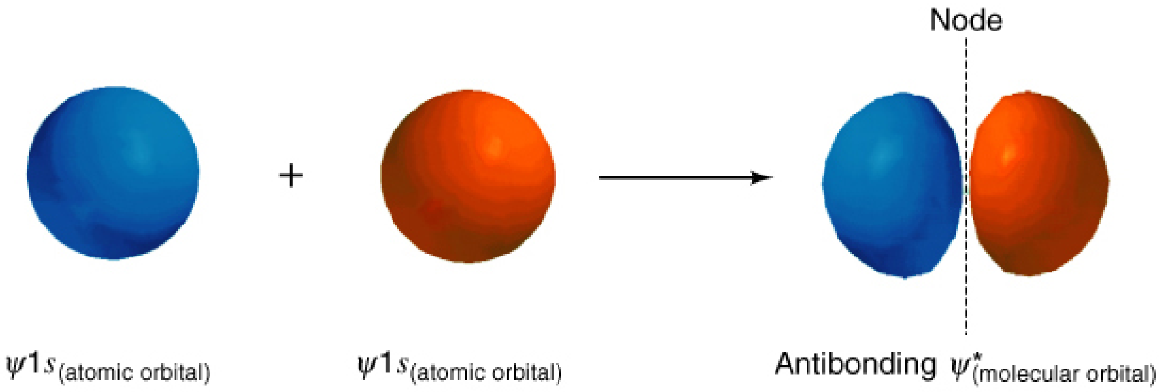


Figure 1.9 The overlapping of two hydrogen 1s atomic orbitals with opposite phase signs (indicated by their different colors) to form an antibonding molecular orbital.

4. **LCAO (*linear combination of atomic orbitals*):**
5. **MO:**

 1) Relative energy of an electron in the bonding MO of the hydrogen molecule is substantially less than its energy in a Ψ_{1s} AO.
 2) Relative energy of an electron in the antibonding MO of the hydrogen molecule is substantially greater than its energy in a Ψ_{1s} AO.

1.11D. Energy Diagram for the Hydrogen Molecule

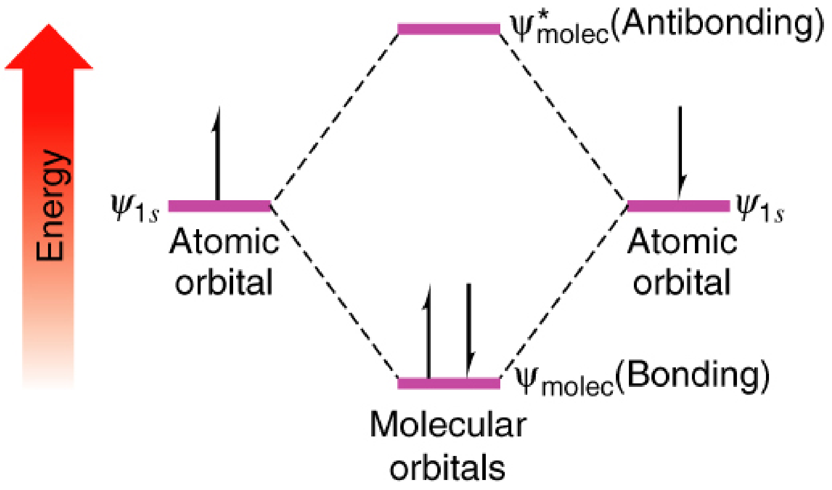
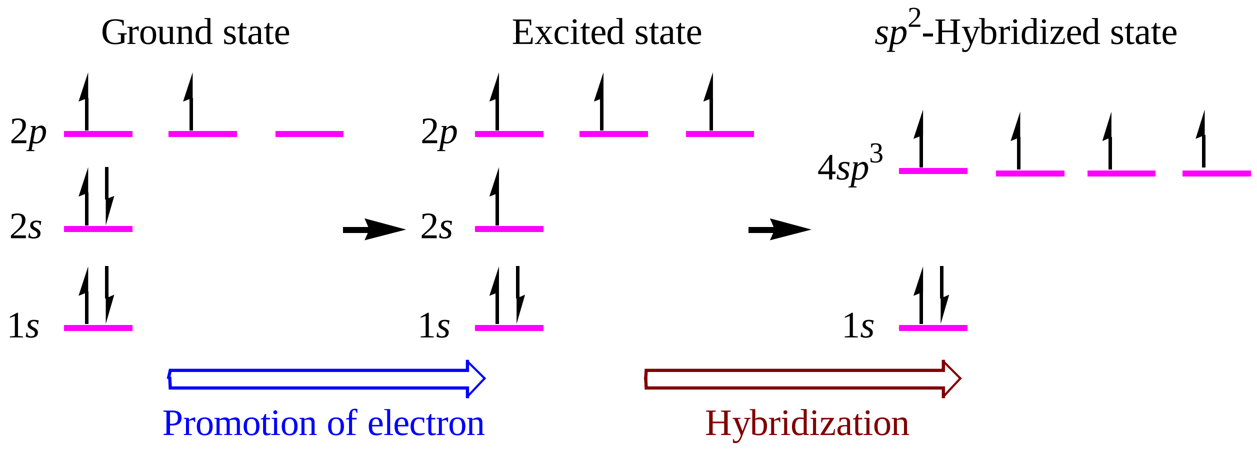


Figure 1.10 Energy diagram for the hydrogen molecule. Combination of two atomic orbitals, Ψ_{1s}, gives two molecular orbitals, Ψ_{molec} and Ψ^*_{molec}. The energy of Ψ_{molec} is lower than that of the separate atomic orbitals, and in the lowest electronic state of molecular hydrogen it contains both electrons.

1.12 THE STRUCTURE OF METHANE AND ETHANE: *sp*^{3} HYBRIDZATION

1. **Orbital hybridization:** A mathematical approach that involves the combining of individual wave functions for s and p orbitals to obtain wave functions for new orbitals ⇒ **hybrid atomic orbitals**



1.12A. The Structure of Methane

1. **Hybridization of AOs of a carbon atom:**

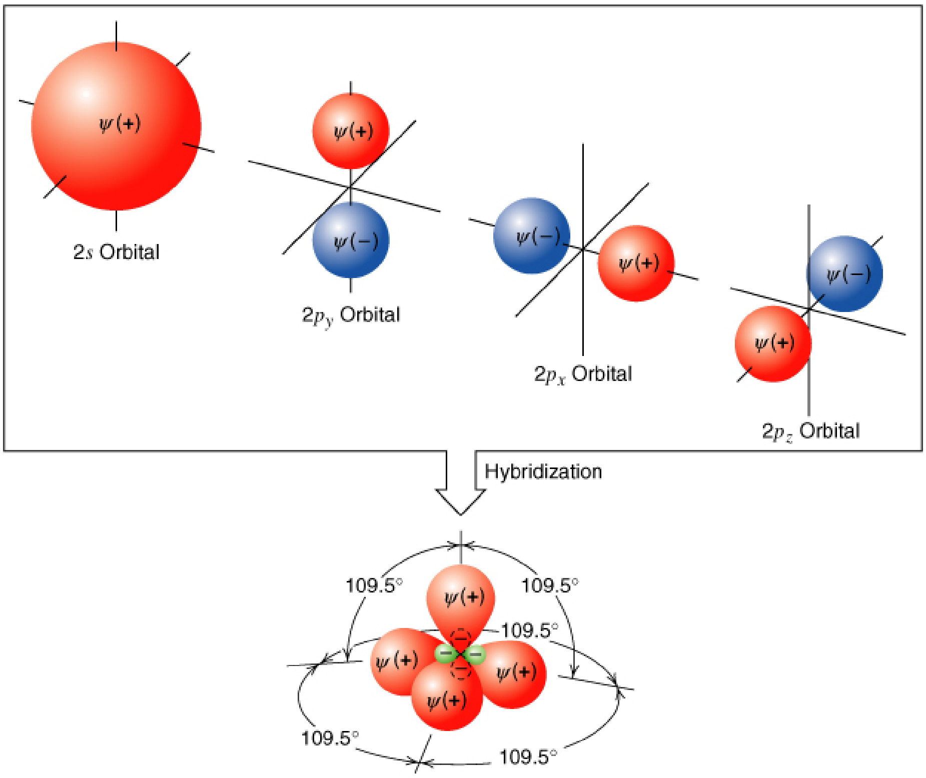


Figure 1.11 **Hybridization of pure atomic orbitals of a carbon atom to produce *sp*^{3} hybrid orbitals.**

2. **The four *sp*^{3} orbitals should be oriented at angles of 109.5° with respect to each other ⇒ an *sp*^{3}-hybridized carbon gives a tetrahedral structure for methane.**

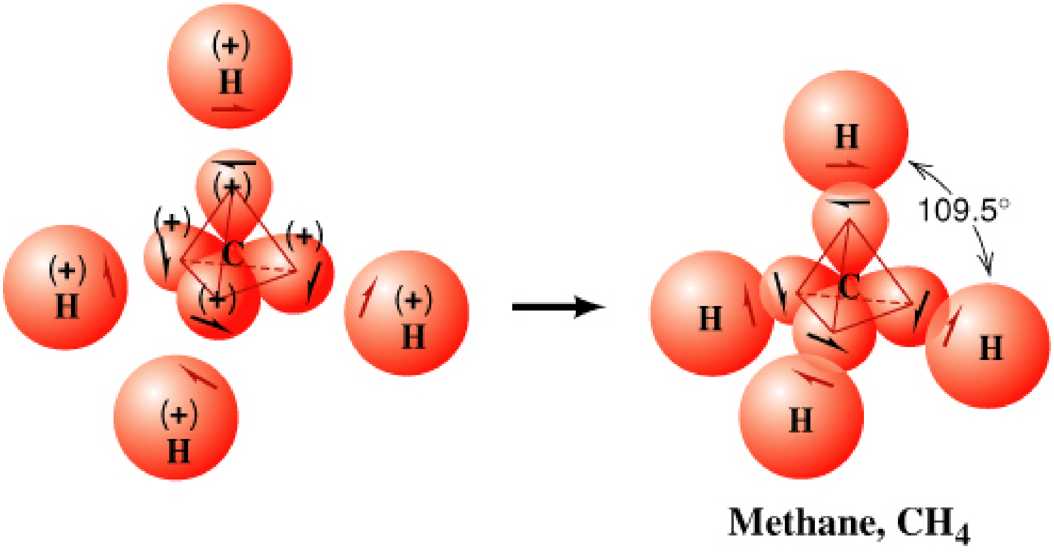


Figure 1.12 **The hypothetical formation of methane from an *sp*^{3}-hybridized carbon atom. In orbital hybridization we combine orbitals, *not* electrons. The electrons can then be placed in the hybrid orbitals as necessary for bond formation, but always in accordance with the Pauli principle of no more than two electrons (with opposite spin) in each orbital. In this illustration we have placed one electron**

in each of the hybrid carbon orbitals. In addition, we have shown only the bonding molecular orbital of each C–H bond because these are the orbitals that contain the electrons in the lowest energy state of the molecule.

3. **Overlap of hybridized orbitals:**

   1) The positive lobe of the sp^3 orbital is large and is extended quite far into space.

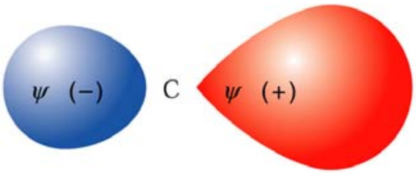


Figure 1.13 The shape of an sp^3 orbital.

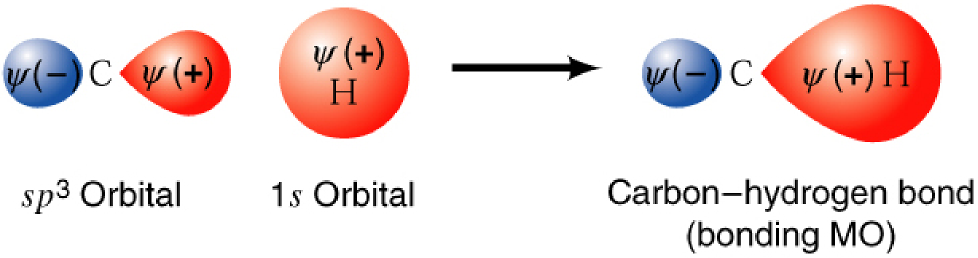


Figure 1.14 Formation of a C–H bond.

   2) **Overlap integral:** a measure of the extent of overlap of orbitals on neighboring atoms.

   3) **The greater the overlap achieved (the larger integral), the stronger the bond formed.**

   4) **The relative overlapping powers of atomic orbitals have been calculated as follows:**

      ***s*: 1.00; *p*: 1.72; *sp*: 1.93; sp^2: 1.99; sp^3: 2.00**

4. **Sigma (σ) bond:**

   1) A bond that is ***circularly symmetrical in cross section when viewed along the bond axis***.

   2) ***All purely single bonds are sigma bonds.***

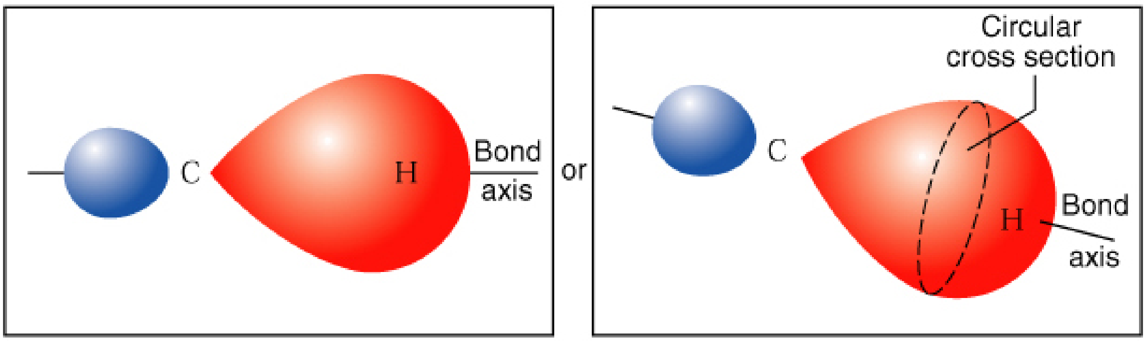


Figure 1.15 A σ (sigma) bond.

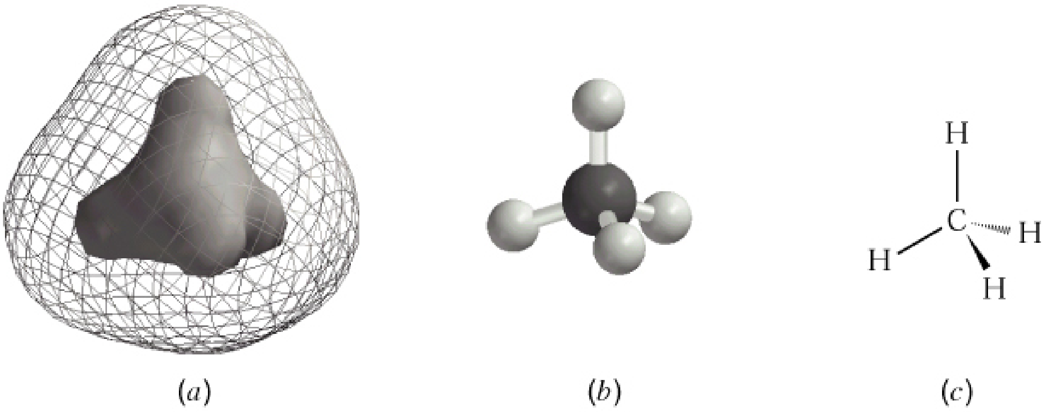


Figure 1.16 (a) In this structure of methane, based on quantum mechanical calculations, the inner solid surface represents a region of high electron density. High electron density is found in each bonding region. The outer mesh surface represents approximately the furthest extent of overall electron density for the molecule. (b) This ball-and-stick model of methane is like the kind you might build with a molecular model kit. (c) This structure is how you would draw methane. Ordinary lines are used to show the two bonds that are in the plane of the paper, a solid wedge is used to show the bond that is in front of the paper, and a dashed wedge is used to show the bond that is behind the plane of the paper.

1.12B. The Structure of Ethane

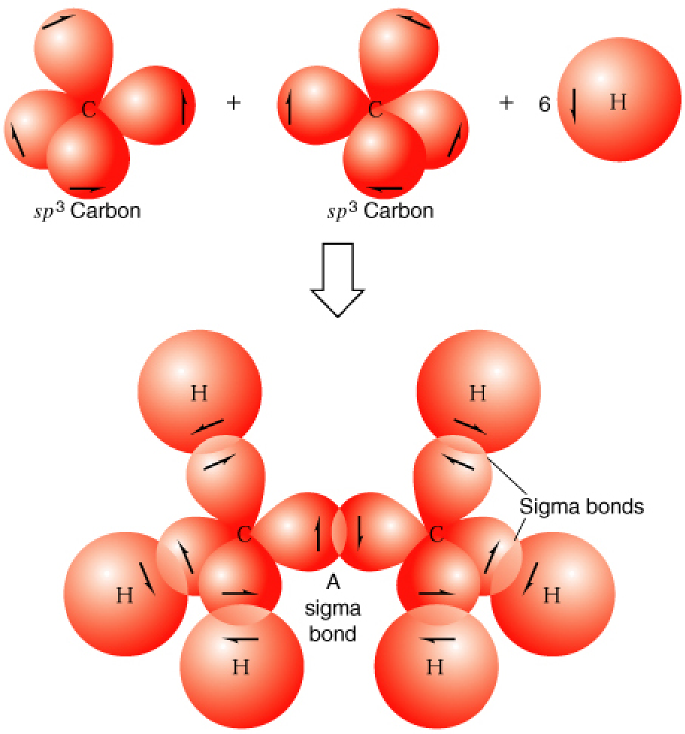


Figure 1.17 The hypothetical formation of the bonding molecular orbitals of ethane from two *sp*^{3}-hybridized carbon atoms and six hydrogen atoms. All of the bonds are sigma bonds. (Antibonding sigma molecular orbitals — are called σ* orbitals — are formed in each instance as well, but for simplicity these are not shown.)

1. **Free rotation about C–C:**

   1) A sigma bond has cylindrical symmetry along the bond axis ⇒ **rotation of groups joined by a single bond does not usually require a large amount of energy** ⇒ **free rotation**.

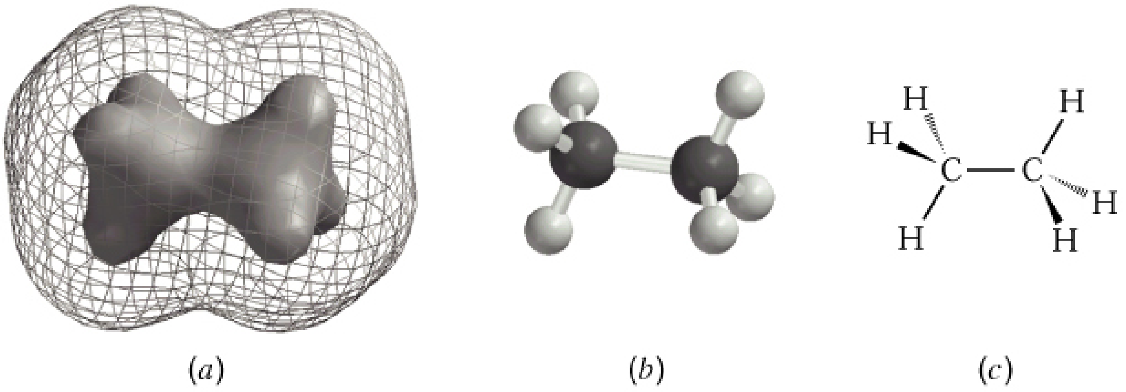
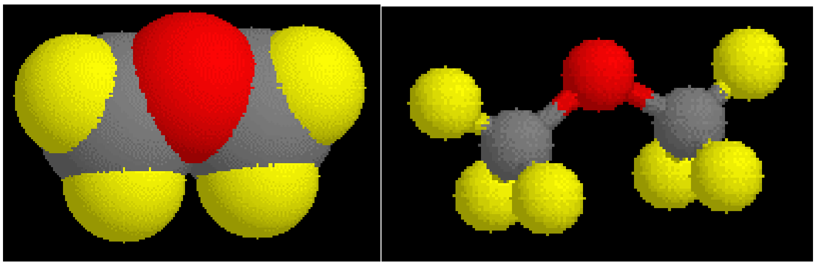


Figure 1.18 (a) In this structure of ethane, based on quantum mechanical calculations, the inner solid surface represents a region of high electron density. High electron density is found in each bonding region. The outer mesh surface represents approximately the furthest extent of overall electron density for the

molecule. (b) A ball-and-stick model of ethane, like the kind you might build with a molecular model kit. (c) A structural formula for ethane as you would draw it using lines, wedges, and dashed wedges to show in three dimensions its tetrahedral geometry at each carbon.

2. **Electron density surface:**

1) An electron density surface shows points in space that happen to have the same electron density.
2) A **"high"** electron density surface (also called a "bond" electron density surface) shows the ***core*** of electron density around each atomic nucleus and regions where neighboring atoms share electrons (covalent bonding regions).
3) A **"low"** electron density surface roughly shows the ***outline*** of a molecule's electron cloud. This surface gives information about molecular shape and volume, and usually looks the same as a van der Waals or space-filling model of the molecule.



Dimethyl ether

1.13 THE STRUCTURE OF ETHENE (ETHYLENE): *sp*^{2} HYBRIDZATION

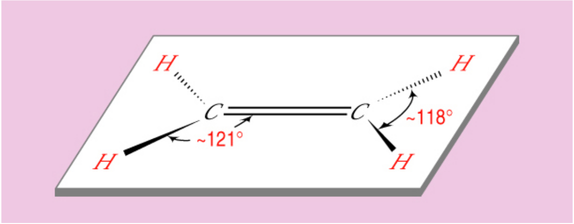


Figure 1.19 The structure and bond angles of ethene. The plane of the atoms is perpendicular to the paper. The dashed edge bonds project behind the plane of the paper, and the solid wedge bonds project in front of the paper.

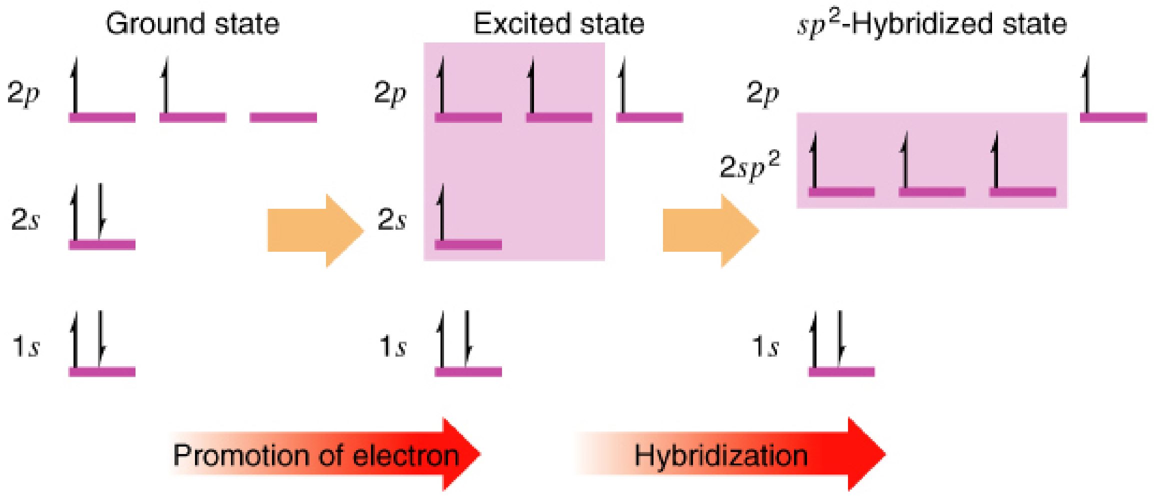


Figure 1.20 A process for obtaining sp^2-hybridized carbon atoms.

1. One 2*p* orbital is left unhybridized.
2. The three sp^2 orbitals that result from hybridization are directed toward the corners of a regular triangle.

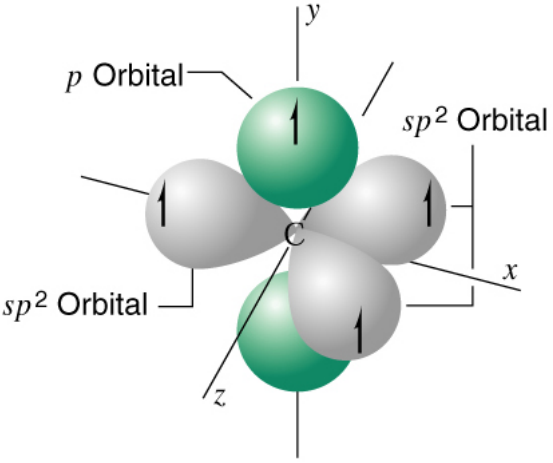


Figure 1.21 An sp^2-hybridized carbon atom.

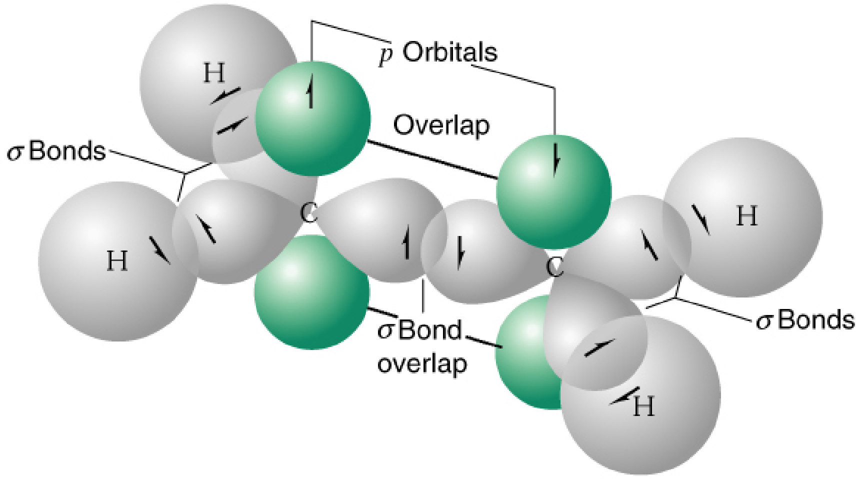


Figure 1.22 A model for the bonding molecular orbitals of ethane formed from

two *sp*^{2}-hybridized carbon atoms and four hydrogen atoms.

3. **The *σ-bond framework*:**

4. **Pi (π) bond:**

   1) The parallel *p* orbitals ***overlap above and below the plane of the σ framework***.
   2) The sideway overlap of *p* orbitals results in the formation of a ***π bond***.
   3) A π bond has a nodal plane passing through the two bonded nuclei and between the π molecular orbital lobes.

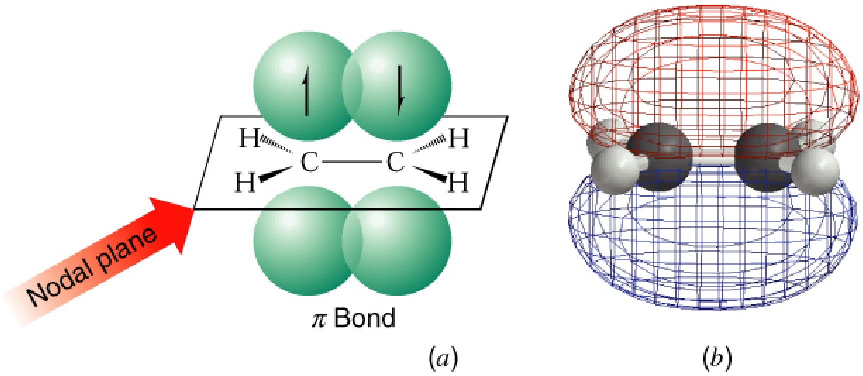


Figure 1.23 (a) A wedge-dashed wedge formula for the sigma bonds in ethane and a schematic depiction of the overlapping of adjacent *p* orbitals that form the π bond. (b) A calculated structure for enthene. The blue and red colors indicate opposite phase signs in each lobe of the π molecular orbital. A ball-and-stick model for the σ bonds in ethane can be seen through the mesh that indicates the π bond.

4. **Bonding and antibonding π molecular orbitals:**

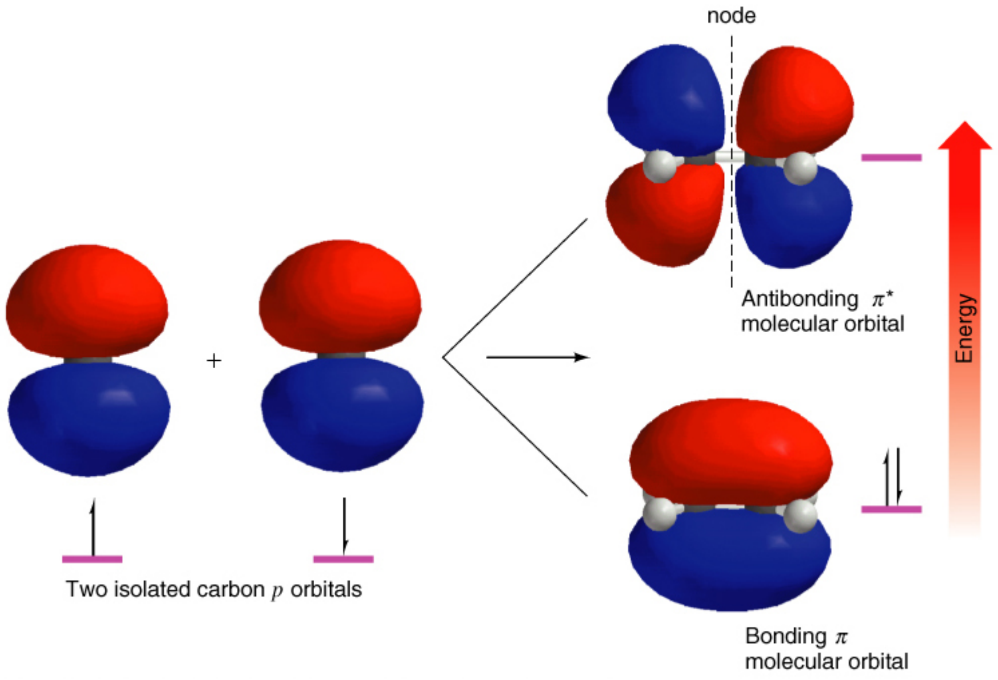
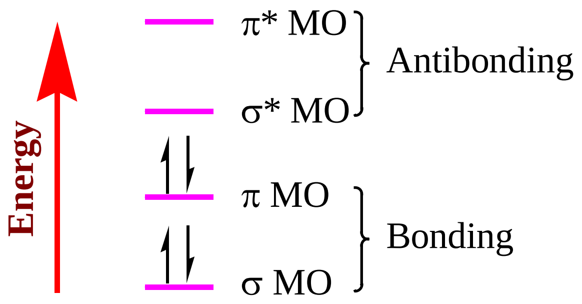


Figure 1.24 How two isolated carbon *p* orbitals combine to form two π (pi) molecular orbitals. The bonding MO is of lower energy. The higher energy antibonding MO contains an additional node. (Both orbitals have a node in the plane containing the C and H atoms.)

1) The bonding π orbital is the lower energy orbital and contains both π electrons (with opposite spins) in the ground state of the molecule.
2) The antibonding π* orbital is of higher energy, and it is not occupied by electrons when the molecule is in the ground state.



1.13A. Restricted Rotation and the Double Bond

1. There is a large energy barrier to rotation associated with groups joined by a double bond.

1) Maximum overlap between the *p* orbitals of a π bond occurs when the axes of the

p orbitals are exactly parallel ⇒ Rotation one carbon of the double bond 90° breaks the π bond.

2) The strength of the π bond is 264 KJ mol^{-1} (63.1 Kcal mol^{-1})⇒ the rotation barrier of double bond.

3) The rotation barrier of a C–C single bond is 13-26 KJ mol^{-1} (3.1-6.2 Kcal mol^{-1}).

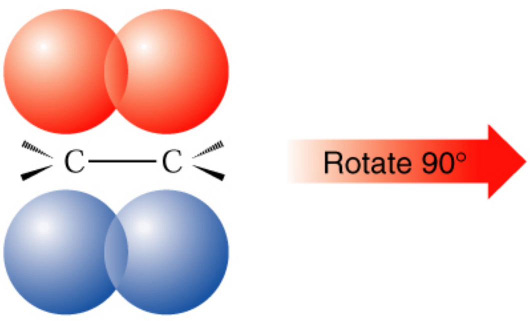
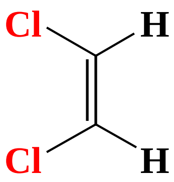
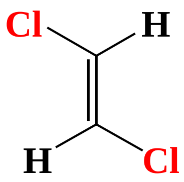
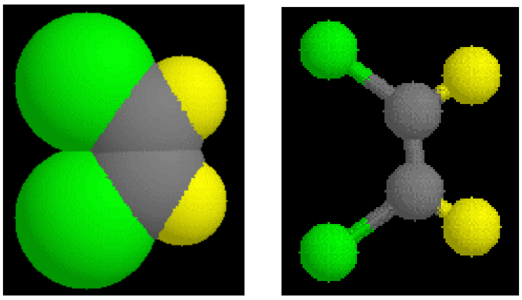


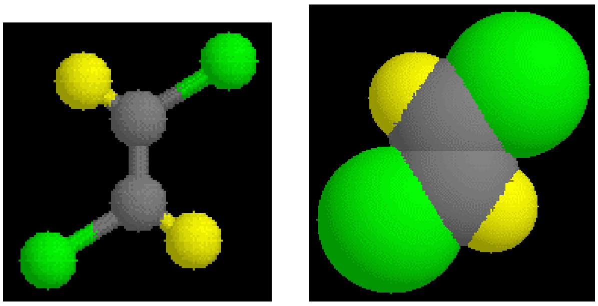
Figure 1.25 A stylized depiction of how rotation of a carbon atom of a double bond through an angle of 90° results in breaking of the π bond.

1.13B. *Cis-Trans* Isomerism









***cis*-1,2-Dichloroethene** ***trans*-1,2-Dichloroethene**

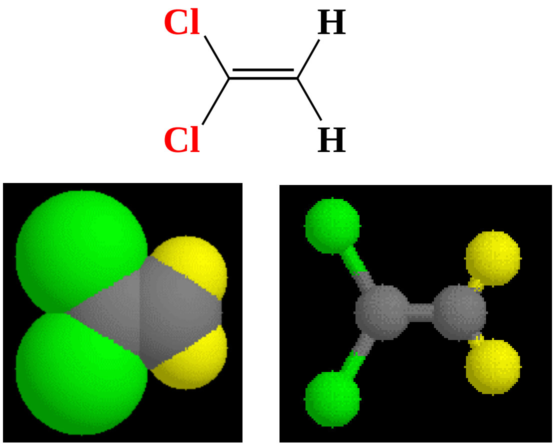
1. Stereoisomers

1) *cis*-1,2-Dichloroethene and *trans*-1,2-dichloroethene are ***non-superposable*** ⇒ Different compounds ⇒ ***not constitutional isomers***

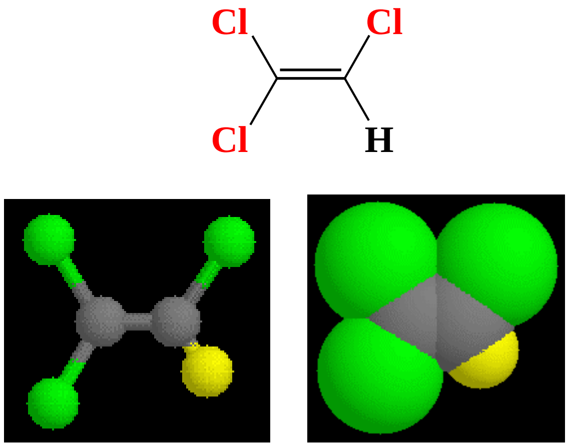
2) Latin: *cis*, on the same side; *trans*, across.

3) ***Stereoisomers*** ⇒ **differ only in the arrangement of their atoms in space**.

4) If one carbon atom of the double bond bears two identical groups ⇒ ***cis-trans* isomerism is not possible**.



1,1-Dichloroethene
(no *cis-trans* isomerism)



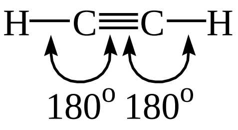
1,1,2-Trichloroethene
(no *cis-trans* isomerism)

1.14 THE STRUCTURE OF ETHYNE (ACETYLENE): *sp* HYBRIDZATION

1. **Alkynes**

H—C≡C—H
Ethyne
(acetylene)
(C_2H_2)

H_3C—C≡C—H
Propyne
(C_2H_2)



2. ***sp* Hybridization:**

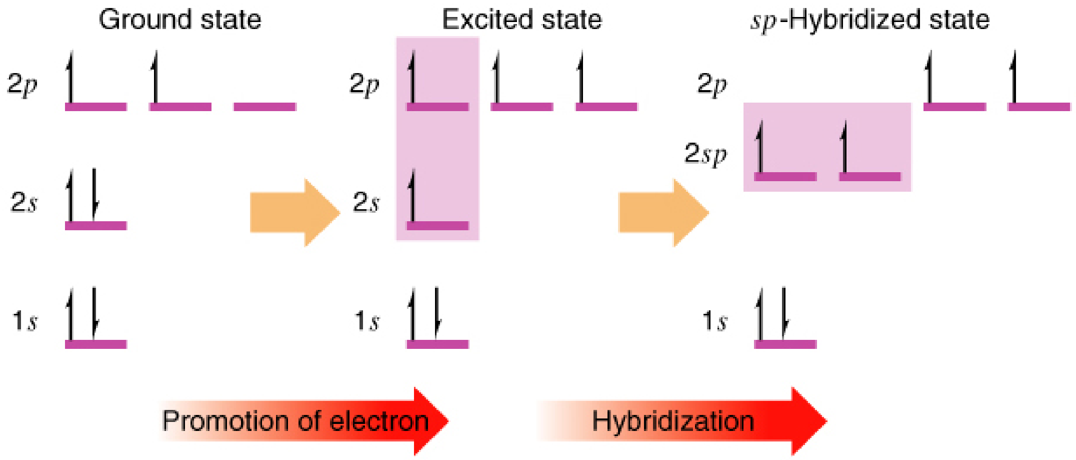


Figure 1.26 A process for obtaining *sp*-hybridized carbon atoms.

3. The *sp* hybrid orbitals have their large positive lobes oriented at an angle of 180° with respect to each other.

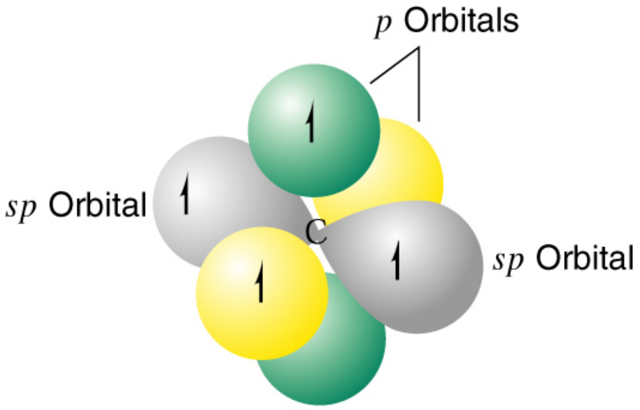


Figure 1.27 An *sp*-hybridized carbon atom.

4. **The carbon-carbon triple bond consists of two π bonds and one σ bond.**

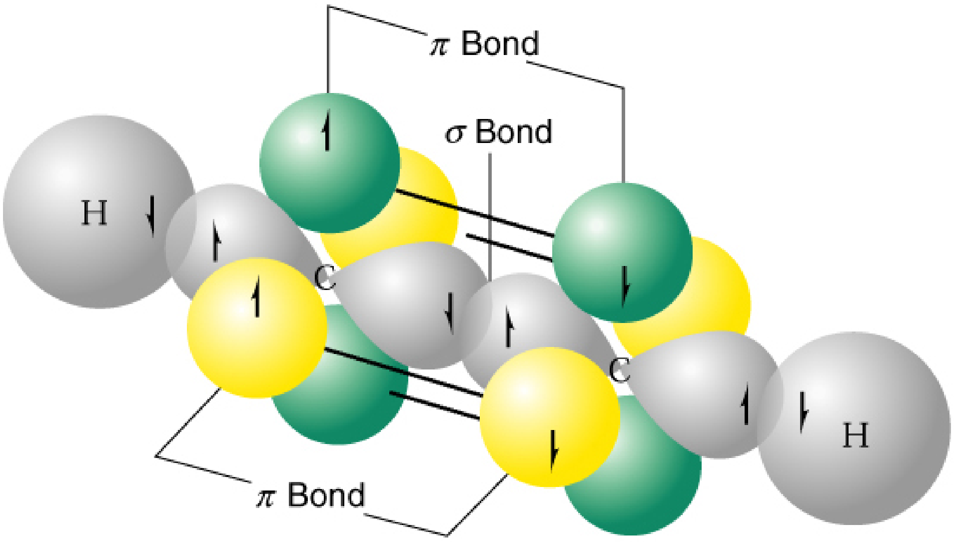


Figure 1.28 Formation of the bonding molecular orbitals of ethyne from two *sp*-hybridized carbon atoms and two hydrogen atoms. (Antibonding orbitals are formed as well but these have been omitted for simplicity.)

5. **Circular symmetry** exists along the length of a triple bond (**Fig. 1.29b**) ⇒ **no restriction of rotation** for groups joined by a triple bond.

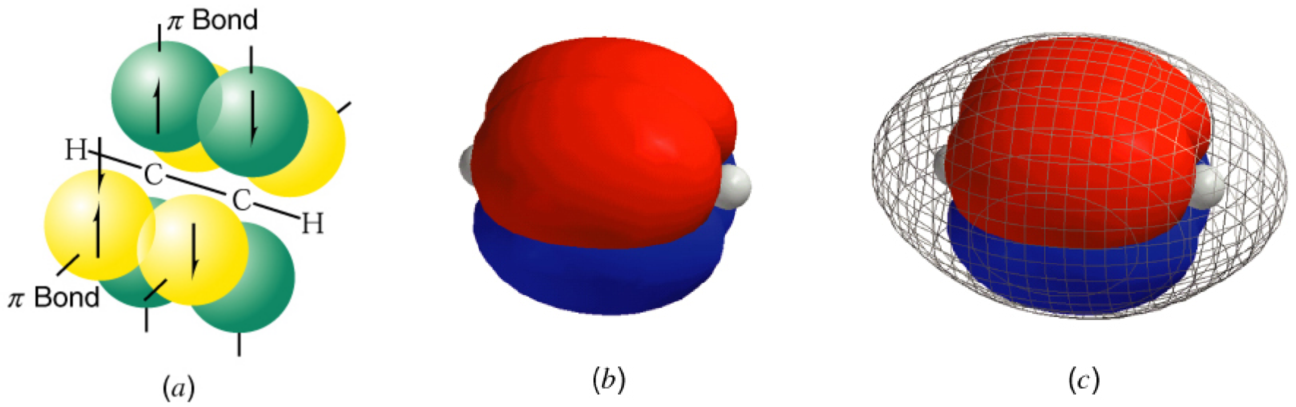


Figure 1.29 (a) The structure of ethyne (acetylene) showing the sigma bond framework and a schematic depiction of the two pairs of *p* orbitals that overlap to form the two π bonds in ethyne. (b) A structure of ethyne showing calculated π molecular orbitals. Two pairs of π molecular orbital lobes are present, one pair for each π bond. The red and blue lobes in each π bond represent opposite phase signs. The hydrogenatoms of ethyne (white spheres) can be seen at each end of the structure (the carbon atoms are hidden by the molecular orbitals). (c) The mesh surface in this structure represents approximately the furthest extent of overall electron density in ethyne. Note that the overall electron density (but not the π bonding electrons) extends over both hydrogen atoms.

1.14A. Bond lengths of Ethyne, Ethene, and Ethane

1. **The shortest C–H bonds are associated with those carbon orbitals with the greatest *s* character.**

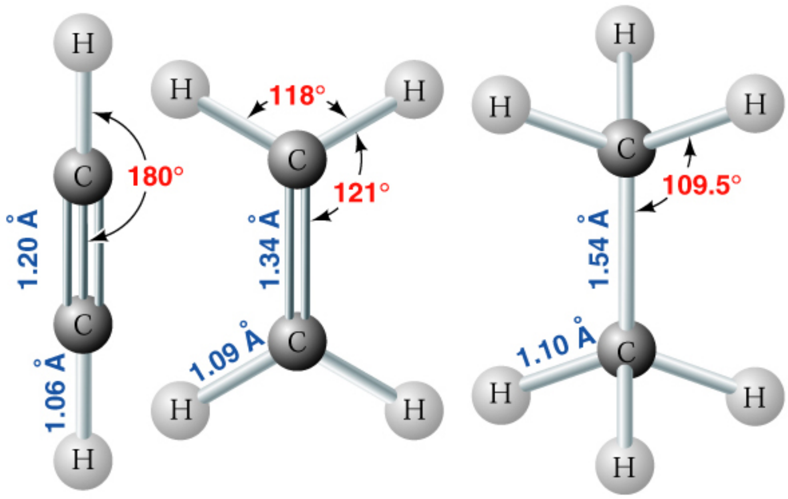


Figure 1.30 Bond angles and bond lengths of ethyne, ethene, and ethane.

1.15 A SUMMARY OF IMPORTANT CONCEPTS THAT COME FROM QUANTUM MECHANICS

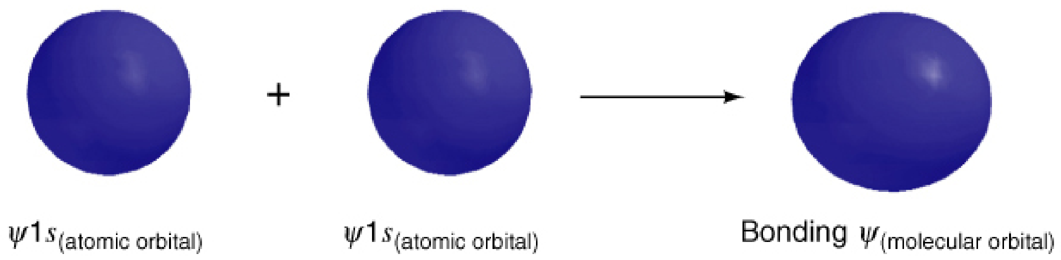
1.15A. Atomic orbital (AO):

1. AO corresponds to a region of space with high **probability** of finding an electron.
2. **Shape** of orbitals: *s*, *p*, *d*
3. Orbitals can hold a maximum of two electrons when their spins are paired.
4. Orbitals are described by a wave function, ψ.
5. **Phase sign** of an orbital: "+", "–"

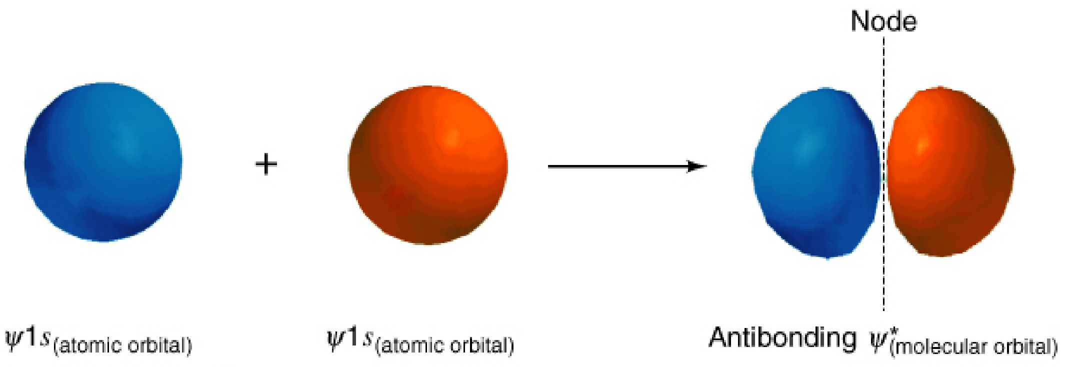
1.15B. Molecular orbital (MO):

1. MO corresponds to a region of space encompassing two (or more) nuclei where electrons are to be found.

1) **Bonding molecular orbital:** ψ



2) **Antibonding molecular orbital:** ψ*



3) **Node:**

4) **Energy of electrons:**

5) **Number of molecular orbitals:**

6) **Sigma bond (σ):**

7) **Pi bond (π):**

1.15C. Hybrid atomic orbitals:

1. **sp^3 orbitals ⇒ tetrahedral**
2. **sp^2 orbitals ⇒ trigonal planar**
3. **sp orbitals ⇒ linear**

1.16 MOLECULAR GEOMETRY: THE VALENCE SHELL ELECTRON-PAIR REPULSION (VSEPR) MODEL

1. **Consider all valence electron pairs of the "central" atom —— bonding pairs, nonbonding pairs** (**lone pairs, unshared pairs**)
2. **Electron pairs repel each other ⇒ The electron pairs of the valence tend to stay as far apart as possible**.

1) The **geometry** of the molecule —— considering "**all**" of the electron pairs.

2) The **shape** of the molecule —— referring to the "**positions**" of the "**nuclei** (or **atoms**)".

1.16A Methane

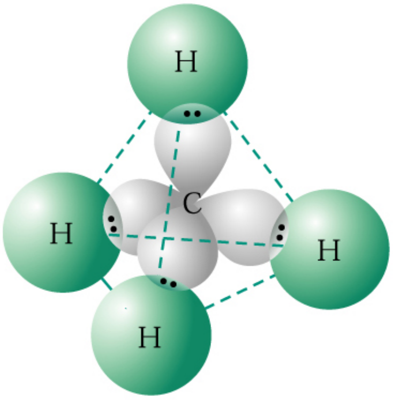


Figure 1.31 A tetrahedral shape for methane allows the maximum separation of the four bonding electron pairs.

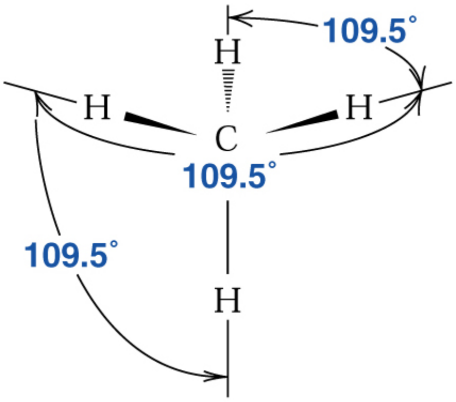
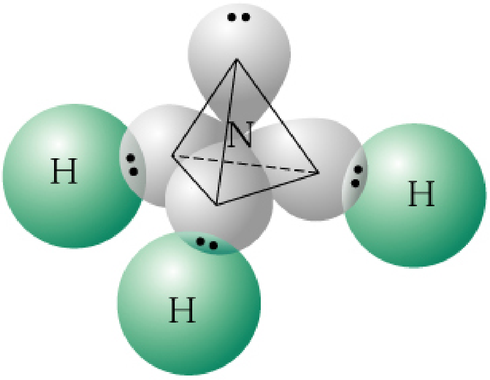


Figure 1.32 The bond angles of methane are 109.5°.

1.16B Ammonia



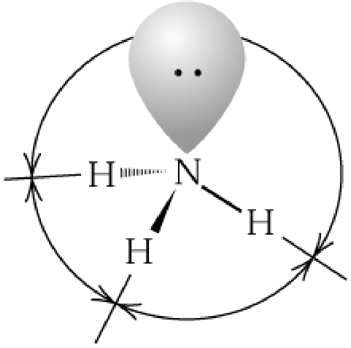
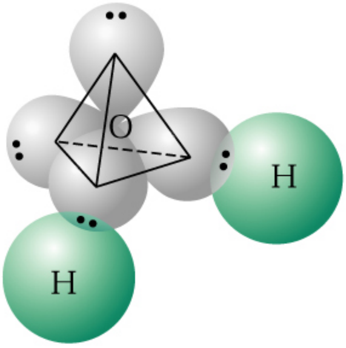


Figure 1.33 The tetrahedral arrangement of the electron pairs of an ammonia molecule that results when the nonbonding electron pair is considered to occupy one corner. This arrangement of electron pairs explains the trigonal pyramidal shape of the NH_3 molecule.

1.16C Water



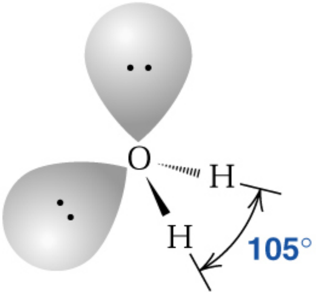


Figure 1.34 An approximately tetrahedral arrangement of the electron pairs for a molecule of water that results when the pair of nonbonding electrons are considered to occupy corners. This arrangement accounts for the angular shape of the H_2O molecule.

1.16D Boron Trifluoride

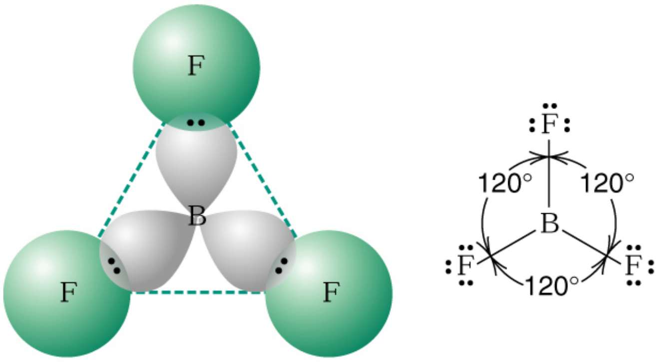
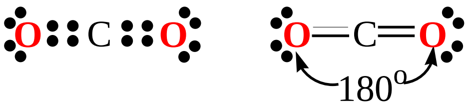


Figure 1.35 The triangular (trigonal planar) shape of boron trifluoride maximally separates the three bonding pairs.

1.16E Beryllium Hydride

Linear geometry of BeH_2

1.16F Carbon Dioxide



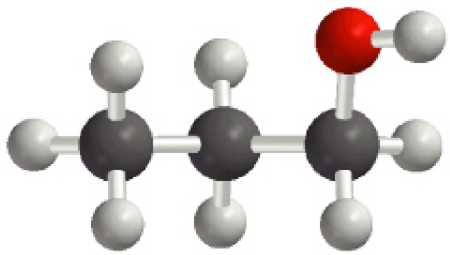
The four electrons of each double bond act as a single unit and are maximally separated from each other.

Table 1.4 Shapes of Molecules and Ions from VSEPR Theory

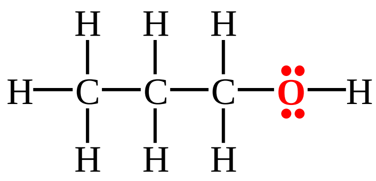
Number of Electron Pairs at Central Atom: Bonding	Nonbonding	Total	Hybridization State of Central Atom	Shape of Molecule or Ion[a]	Examples
2	0	2	*sp*	Linear	BeH_2
3	0	3	sp^2	Trigonal planar	BF_3, CH_3^+
4	0	4	sp^3	Tetrahedral	CH_4, NH_4^+
3	1	4	$\sim sp^3$	Trigonal pyramidal	NH_3, CH_3^-
2	2	4	$\sim sp^3$	Angular	H_2O

[a] Referring to positions of atoms and excluding nonbonding pairs.

1.17 REPRESENTATION OF STRUCTURAL FORMULAS



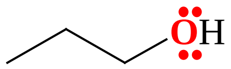
Ball-and-stick model



Dash formula

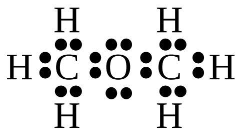
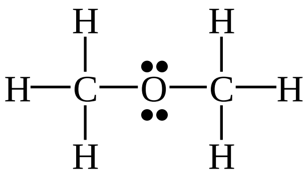
$CH_3CH_2CH_2\ddot{\underset{..}{O}}H$

Condensed formula



Bond-line formula

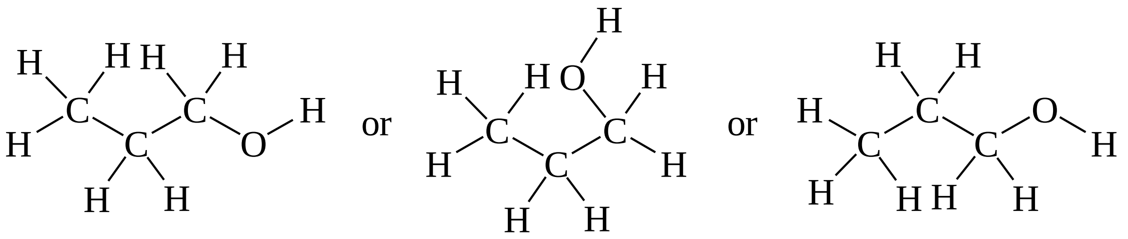
Figure 1.36 Structural formulas for propyl alcohol.

 =  = $CH_3\ddot{\underset{..}{O}}CH_3$

Dot structure **Dash formula** **Condensed formula**

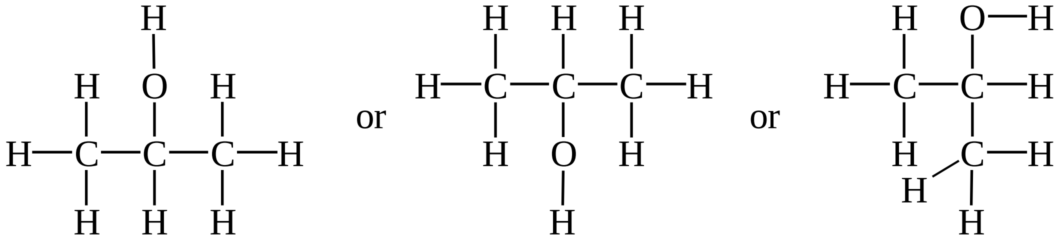
1.17A Dash Structural Formulas

1. **Atoms joined by single bonds can rotate relatively freely with respect to one another.**



Equivalent dash formulas for propyl alcohol ⇒ same **connectivity** of the atoms

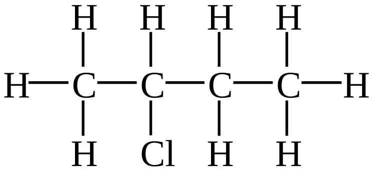
2. ***Constitutional isomers have different connectivity and, therefore, must have different structural formulas.***
3. Isopropyl alcohol is a **constitutional isomer** of propyl alcohol.

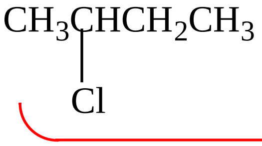


Equivalent dash formulas for isopropyl alcohol ⇒ same **connectivity** of the atoms

4. Do not make the error of writing several equivalent formulas.

1.17B Condensed Structural Formulas

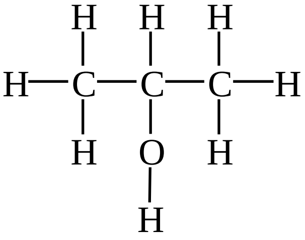


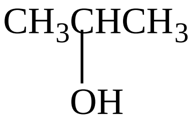


or $CH_3CHClCH_2CH_3$

Dash formulas

Condensed formulas





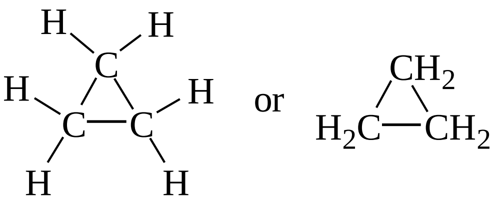
$CH_3CH(OH)CH_3$

$CH_3CHOHCH_3$ or $(CH_3)_2CHOH$

Dash formulas

Condensed formulas

1.17C Cyclic Molecules



Formulas for cyclopropane

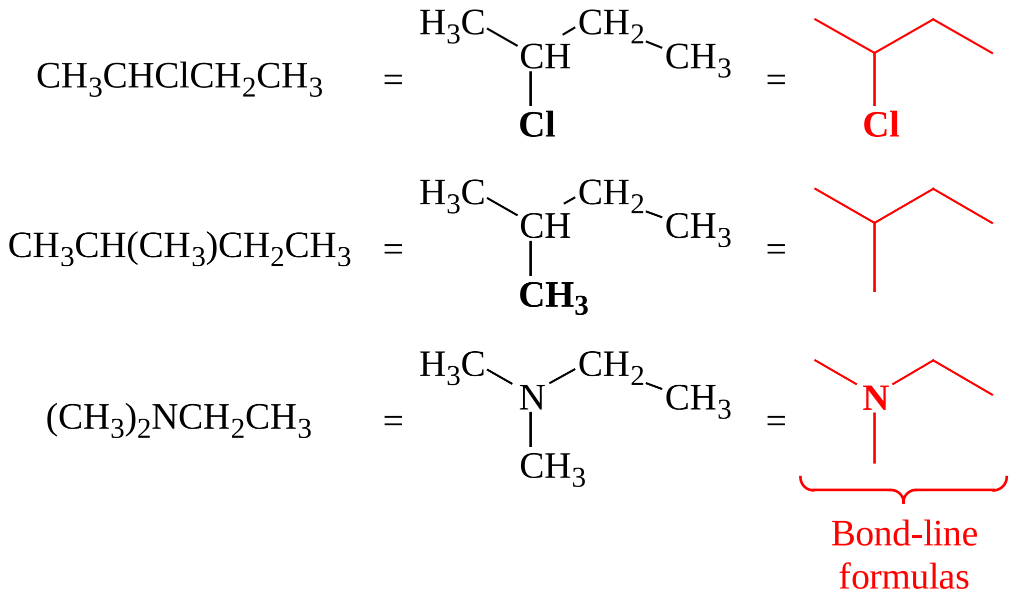
1.17D Bond-Line Formulas (shorthand structure)

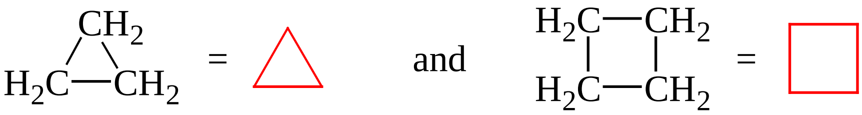
1. Rules for shorthand structure:

1) Carbon atoms are not usually shown ⇒ intersections, end of each line

2) Hydrogen atoms bonded to C are not shown.

3) All atoms other than C and H are indicated.





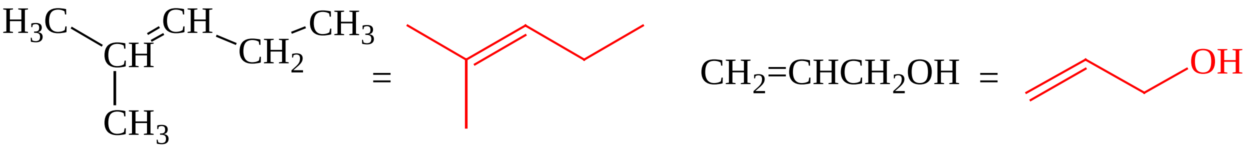
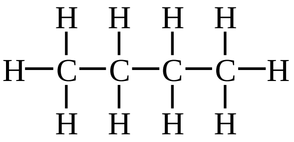
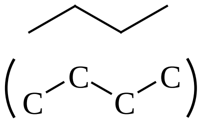
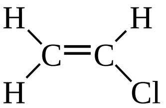
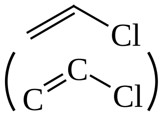
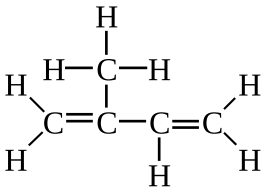
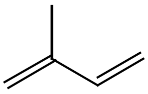


Table 1.5 Kekulé and shorthand structures for several compounds

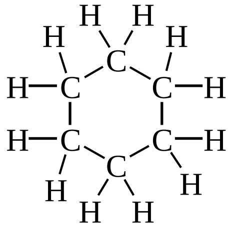
Compound	Kekulé structure	Shorthand structure
Butane, C_4H_{10}		
Chloroethylene (vinyl chloride), C_2H_3Cl		

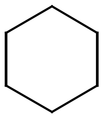
2-Methyl-1,3-butadiene (isoprene), C_5H_8



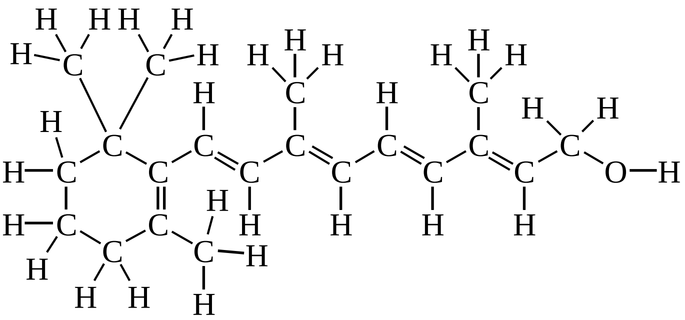


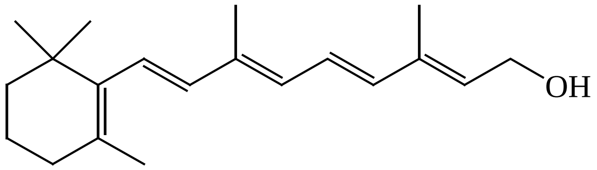
Cyclohexane, C_6H_{12}



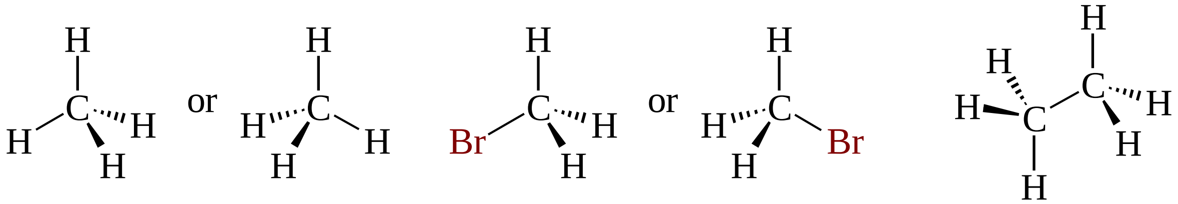


Vitamin A, $C_{20}H_{30}O$





1.17E Three-Dimensional Formulas



Methane **Bromomethane** **Ethane**

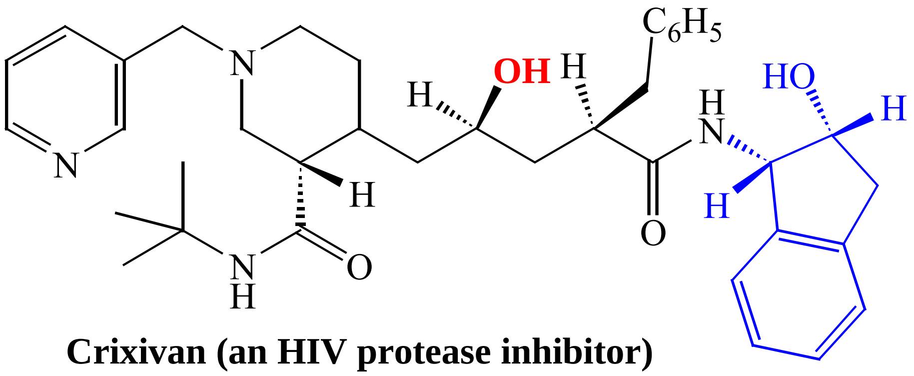
Bromo-chloromethane **Bromo-chloro-iodomethane**

Figure 1.37 Three-dimensional formulas using wedge-dashed wedge-line formulas.

REPRESENTATIVE CARBON COMPOUNDS: FUNCTIONAL GROUPS, INTERMOLECULAR FORCES, AND INFRARED (IR) SPECTROSCOPY

Structure Is Everything

1. The three-dimensional structure of an organic molecule and the functional groups it contains determine its biological function.
2. **Crixivan**, a drug produced by Merck and Co. (the world's premier drug firm, $1 billion annual research spending), is widely used in the fight against AIDS (acquired immune deficiency syndrome).



Crixivan (an HIV protease inhibitor)

1) Crixivan inhibits an enzyme called HIV (human immunodeficiency virus) protease.
2) Using computers and a process of rational chemical design, chemists arrived at a basic structure that they used as a starting point (**lead compound**).
3) Many compounds based on this **lead** are synthesized then until a compound had **optimal potency** as a drug has been found.
4) Crixivan interacts in a highly specific way with the three-dimensional structure of HIV protease.
5) A critical requirement for this interaction is the **hydroxyl** (**OH**) group near the center of Crixivan. This hydroxyl group of Crixivan mimics the true chemical intermediate that forms when HIV protease performs its task in the AIDS virus.
6) By having a higher affinity for the enzyme than its natural reactant, Crixivan ties

up HIV protease by binding to it (**suicide inhibitor**).

7) Merck chemists modified the structures to increase their **water solubility** by introducing a **side chain**.

2.1 Carbon–Carbon Covalent Bonds

1. Carbon forms strong covalent bonds to other carbons, hydrogen, oxygen, sulfur, and nitrogen.
   1) Provides the necessary versatility of structure that makes possible the vast number of different molecules required for complex living organisms.
2. ***Functional groups*:**

2.2 Hydrocarbons: Representative Alkanes, Alkenes, Alkynes, and Aromatic Compounds

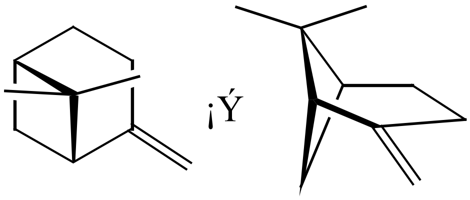
1. **Saturated compounds:** compounds contain the maximum number of **H** atoms.
2. **Unsaturated compounds:**

2.2A Alkanes

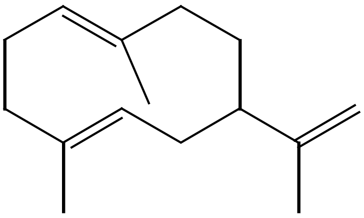
1. The principal sources of alkanes are natural gas and petroleum.
2. Methane is a major component in the atmospheres of Jupiter (木星), Saturn (土星), Uranus (天王星), and Neptune (海王星).
3. *Methanogens*, may be the Earth's oldest organisms, produce methane from carbon dioxide and hydrogen. They can survive only in an anaerobic (i.e., oxygen-free) environment and have been found in ocean trenches, in mud, in sewage, and in cow's stomachs.

2.2B ALKENES

1. **Ethene** (**ethylene**): US produces 30 billion pounds (~1,364 萬噸) each year.
   1) Ethene is produced naturally by fruits such as tomatoes and bananas as a **plant hormone** for the ripening process of these fruits.
   2) Ethene is used as a starting material for the synthesis of many industrial compounds, including ethanol, ethylene oxide, ethanal (acetaldehyde), and polyethylene (PE).
2. **Propene** (**propylene**): US produces 15 billion pounds (~682 萬噸) each year.
   1) Propene is used as a starting material for the synthesis of acetone, cumene (isopropylbenzene), and polypropylene (PP).
3. Naturally occurring alkenes:



β-Pinene (**a component of turpentine**)

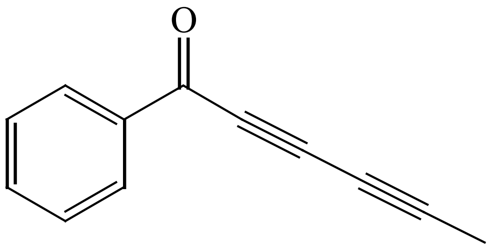


An aphid (**蚜蟲**) **alarm pheromone**

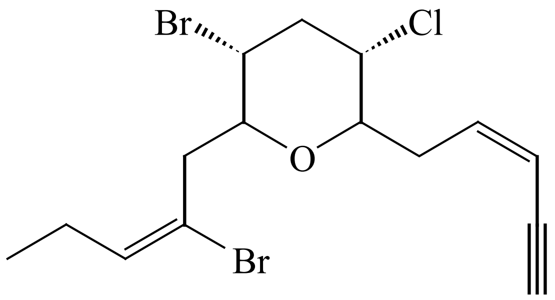
2.2C ALKYNES

1. **Ethyne** (**acetylene**):
   1) Ethyne was synthesized in 1862 by Friedrich Wöhler via the reaction of calcium carbide and water.
   2) Ethyne was burned in carbide lamp (miners' headlamp).
   3) Ethyne is used in welding torches because it burns at a high temperature.

2. Naturally occurring alkynes:
   1) **Capilin**, an antifungal agent.
   2) **Dactylyne**, a marine natural product that is an inhibitor of pentobarbital metabolism.

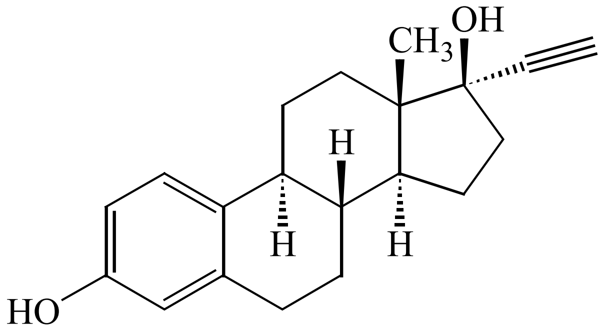


Capilin



Dactylyne

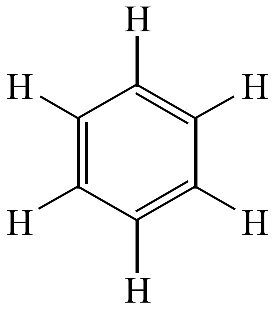
3. Synthetic alkynes:
   1) **Ethinyl estradiol**, its estrogenlike properties have found use in oral contraceptives.



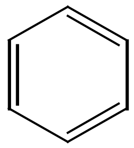
Ethinyl estradiol (**17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol**)

2.2D Benzene: A Representative Aromatic Hydrocarbon

1. Benzene can be written as a six-membered ring with alternating single and double bonds (Kekulé structure).

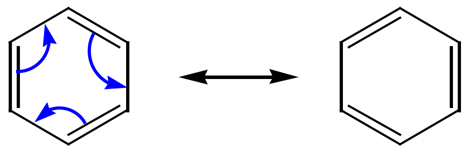


or

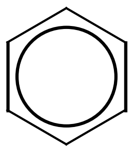


Kekulé structure **Bond-line representation**

2. The C−C bonds of benzene are all the same length (1.39 Å).
3. **Resonance** (valence bond, **VB**) **theory:**



Two contributing Kekulé structures

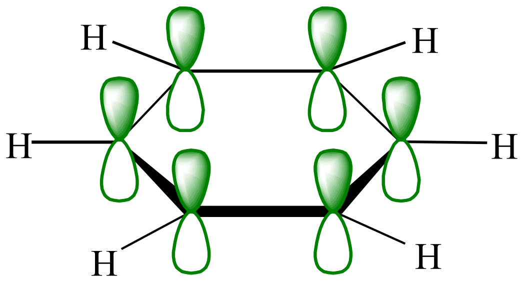


A representation of the resonance hybrid

1) The bonds are not alternating single and double bonds, they are a resonance hybrid ⇒ ***all of the C−C bonds are the same***.

4. **Molecular orbital (MO) theory:**

1) **Delocalization:**



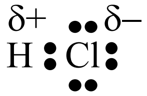
2.3 POLAR COVALENT BONDS

1. **Electronegativity (EN)** is the ability of an element to attract electrons that it is sharing in a covalent bond.

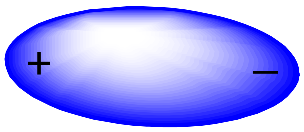
1) When two atoms of different **EN** forms a covalent bond, the electrons are not shared equally between them.

2) The chlorine atom pulls the bonding electrons closer to it and becomes somewhat electron rich ⇒ bears a ***partial negative charge*** (δ–).

3) The hydrogen atom becomes somewhat electron deficient ⇒ bears a ***partial positive charge*** (δ+).



2. **Dipole**:



A dipole

Dipole moment = charge (in esu) x distance (in cm)

$\mu = \boldsymbol{e} \times \boldsymbol{d}$ (**debye**, 1×10^{-18} esu cm)

1) The charges are typically on the order of 10^{-10} esu; the distance 10^{-8} cm.

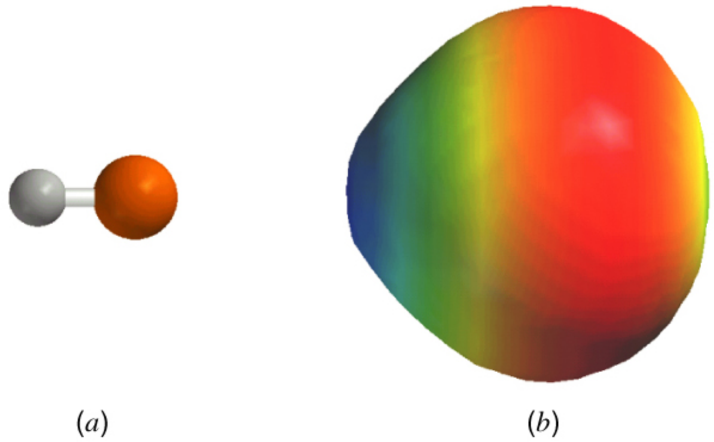


Figure 2.1 a) A ball-and-stick model for hydrogen chloride. B) A calculated electrostatic potential map for hydrogen chloride showing regions of relatively more negative charge in red and more positive charge in blue. Negative charge is clearly localized near the chlorine, resulting in a strong dipole moment for the molecule.

2) The direction of polarity of a polar bond is symbolized by a vector quantity: $+\!\!\longrightarrow$

(**positive end**) $+\!\!\longrightarrow$ (**negative end**) ⇒ H—Cl $+\!\!\longrightarrow$

3) The length of the arrow can be used to indicate the magnitude of the dipole moment.

2.4 Polar and Nonpolar Molecules

1. The **polarity** (**dipole moment**) of a molecule is the vector sum of the dipole moment of each individual **polar bond**.

Table 2.1 Dipole Moments of Some Simple Molecules

Formula	μ (D)	Formula	μ (D)
H_2	0	CH_4	0
Cl_2	0	CH_3Cl	1.87
HF	1.91	CH_2Cl_2	1.55
HCl	1.08	$CHCl_3$	1.02
HBr	0.80	CCl_4	0
HI	0.42	NH_3	1.47
BF_3	0	NF_3	0.24
CO_2	0	H_2O	1.85

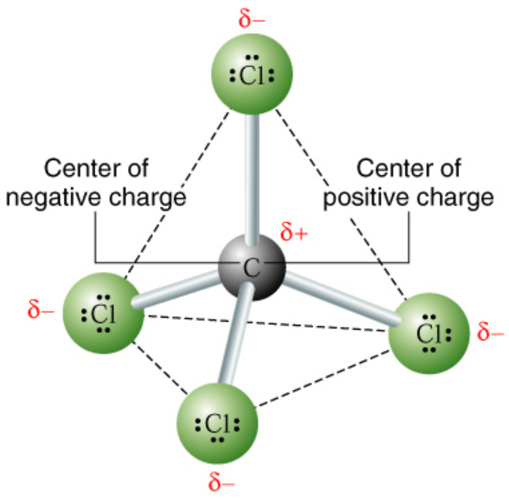


Figure 2.2 Charge distribution in carbon tetrachloride.

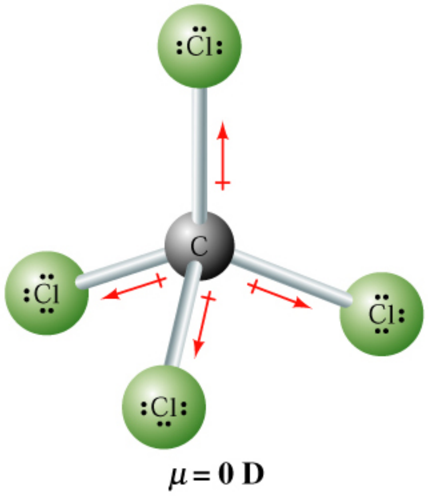


Figure 2.3 A tetrahedral orientation of equal bond moments causes their effects to cancel.

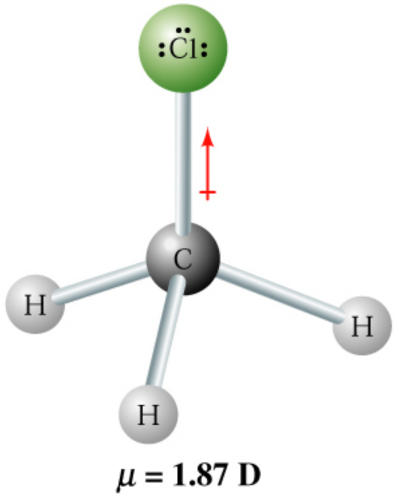


Figure 2.4 The dipole moment of chloromethane arises mainly from the highly polar carbon-chlorine bond.

2. **Unshared pairs** (**lone pairs**) of electrons make large contributions to the dipole moment. (The O–H and N–H moments are also appreciable.)

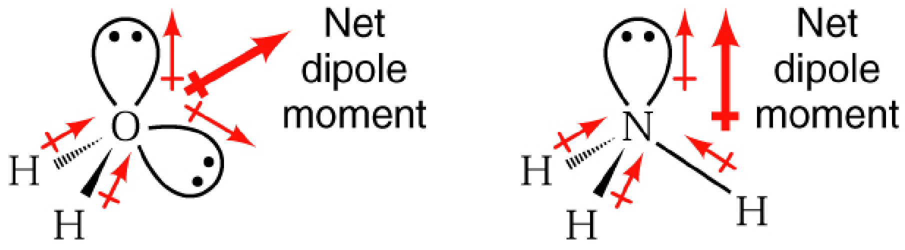


Figure 2.5 Bond moments and the resulting dipole moments of water and ammonia.

2.4A Dipole Moments in Alkenes

1. *Cis-trans* alkenes have different physical properties: m.p., b.p., solubility, and *etc*.
   1) *Cis*-isomer usually has larger dipole moment and hence higher boiling point.

Table 2.2 Physical Properties of Some *Cis-Trans* Isomers

Compound	Melting Point (°C)	Boiling Point (°C)	Dipole Moment (D)
Cis-1,2-Dichloroethene	-80	60	1.90
Trans-1,2-Dichloroethene	-50	48	0
Cis-1,2-Dibromoethene	-53	112.5	1.35
Trans-1,2-Dibromoethene	-6	108	0

2.5 Functional Groups

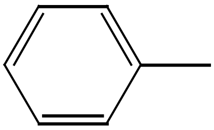
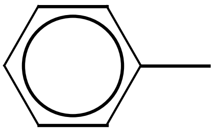
2.5A Alkyl Groups and the Symbol R

Alkane	Alkyl group	Abbreviation
CH_4 **Methane**	CH_3– **Methyl group**	Me–
CH_3CH_3 **Ethane**	CH_3CH_2– or C_2H_5– **Ethyl group**	Et–
$CH_3CH_2CH_3$ **Propane**	$CH_3CH_2CH_2$– **Propyl group**	Pr–
$CH_3CH_2CH_3$ **Propane**	$CH_3\overset{\vert}{C}HCH_3$ or $CH_3\overset{CH_3}{\overset{\vert}{C}}H$– **Isopropyl group**	*i*-Pr–

All of these alkyl groups can be designated by R.

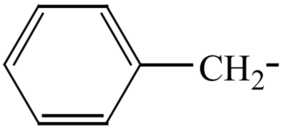
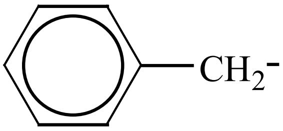
2.5B PHENYL AND BENZYL GROUPS

1. **Phenyl group:**

 or  or C_6H_5– or ϕ– or **Ph**–

or Ar– (if ring substituents are present)

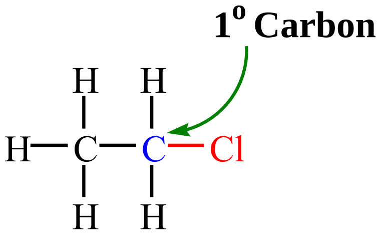
2. **Benzyl group:**

 or  or $C_6H_5CH_2$– or Bn–

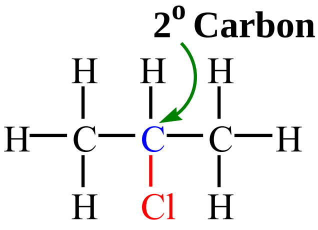
2.6 ALKYL HALIDES OR HALOALKANES

2.6A HALOALKANE

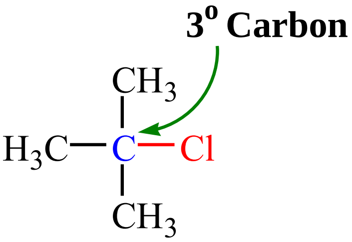
1. **Primary** (1°), **secondary** (2°), or **tertiary** (3°) alkyl halides:



A 1° alkyl chloride



A 2° alkyl chloride

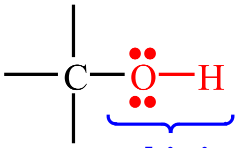


A 3° alkyl chloride

2. **Primary** (1°), **secondary** (2°), or **tertiary** (3°) carbon atoms:

2.7 ALCOHOLS

1. **Hydroxyl group**

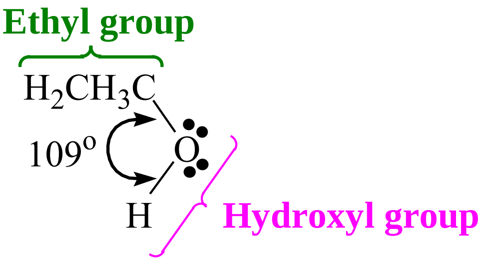


This is the functional group of an alcohol

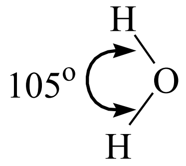
2. Alcohols can be viewed in two ways structurally: (1) as **hydroxyl derivatives** of alkanes and (2) as alkyl derivatives of water.

CH_3CH_3

Ethane

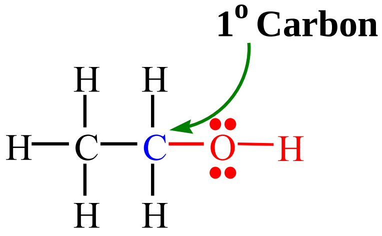


Ethyl alcohol
(ethanol)

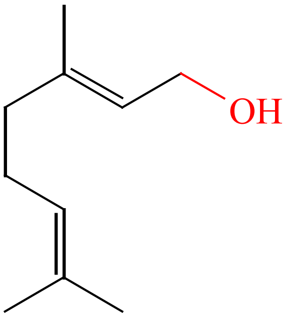


Water

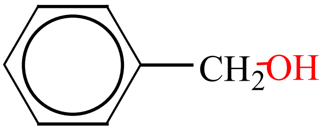
3. **Primary** (1°), **secondary** (2°), or **tertiary** (3°) alcohols:



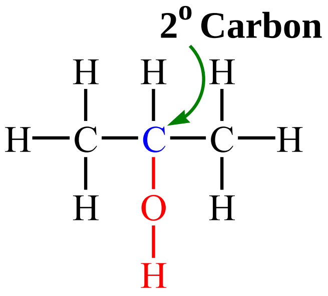
Ethyl alcohol
(a 1° alcohol)



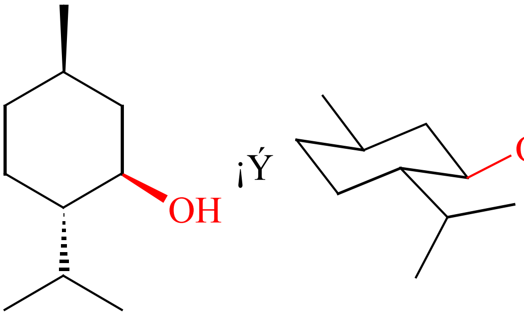
Geraniol
(a 1° alcohol with the odor of roses)



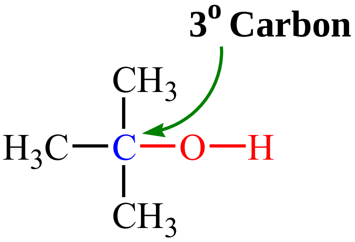
Benzyl alcohol
(a 1° alcohol)



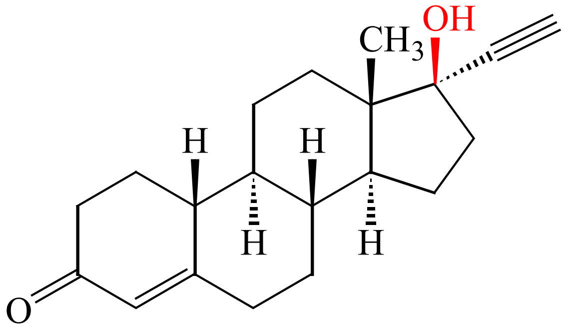
Isopropyl alcohol
(a 2° alcohol)



Menthol
(a 2° alcohol found in pepermint oil)



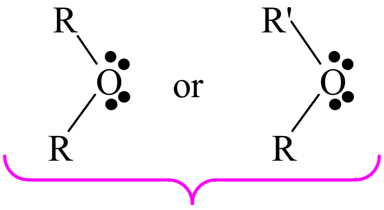
tert-Butyl alcohol
(a 3° alcohol)



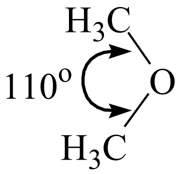
Norethindrone
(an oral contraceptive that contains a 3° alcohol group, as well as a ketone group and carbon-carbon double and triple bonds)

2.8 ETHERS

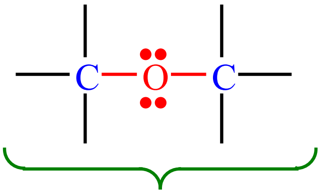
1. Ethers can be thought of as dialkyl derivatives of water.



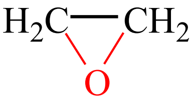
General formula for an ether



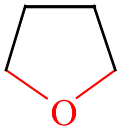
Dimethyl ether
(a typical ether)



The functional of an ether



Ethylene oxide

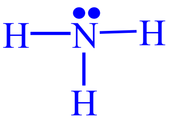


Tetrahydrofuran (THF)

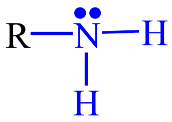
Two cyclic ethers

2.9 AMINES

1. Amines can be thought of as **alkyl derivatives** of **ammonia**.

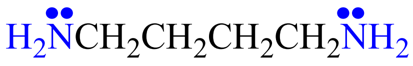


Ammonia



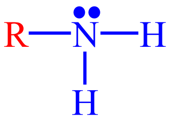
An amine

Amphetamine
(a dangerous stimulant)

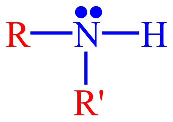


Putrescine
(found in decaying meat)

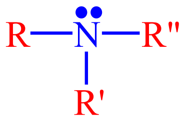
2. **Primary** (1°), **secondary** (2°), or **tertiary** (3°) amines:



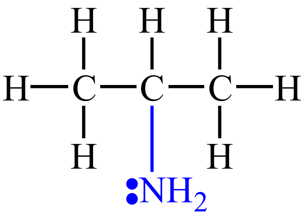
A primary (1°) amine



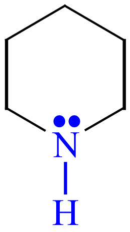
A secondary (2°) amine



A tertiary (3°) amine



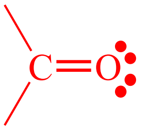
Isopropylamine
(a 1° amine)



Piperidine
(a cyclic 2° amine)

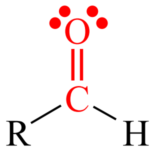
2.10 ALDEHYDES AND KETONES

2.10A CARBONYL GROUP



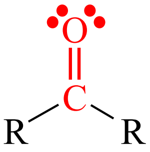
The carbonyl group

Aldehyde

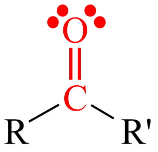


R may also be H

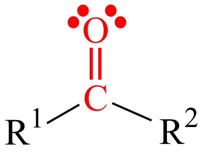
Ketone



or

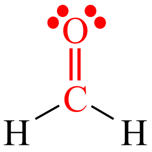


or

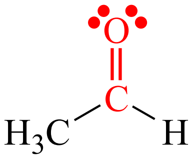


1. Examples of aldehydes and ketones:

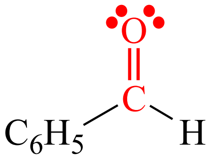
Aldehydes:



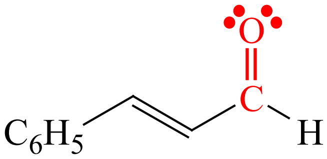
Formaldehyde



Acetaldehyde

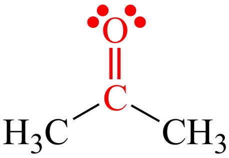


Benzaldehyde

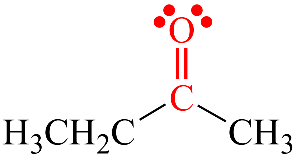


trans-Cinnamaldehyde (present in cinnamon)

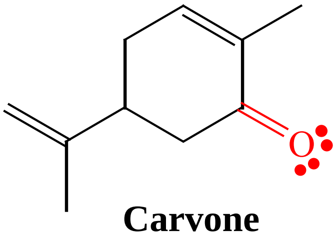
Ketones:



Acetone

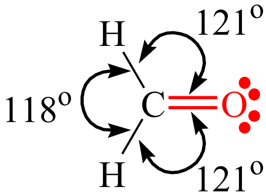


Ethyl methyl ketone



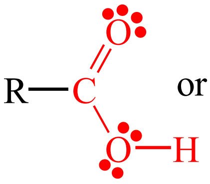
Carvone (from spearmint)

2. Aldehydes and ketones have a trigonal plannar arrangement of groups around the carbonyl carbon atom. The carbon atom is sp^2 hybridized.

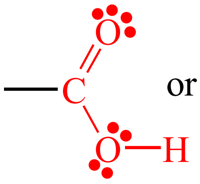


2.11 CARBOXYLIC ACIDS, AMIDES, AND ESTERS

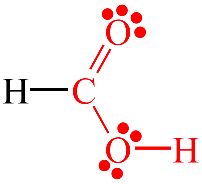
2.11A CARBOXYLIC ACIDS

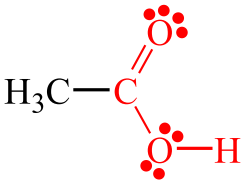
 or RCO_2H or RCOOH

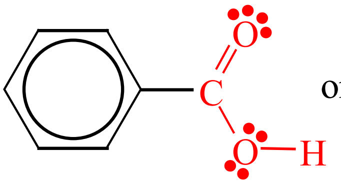
A carboxylic acid

 or —CO_2H or —COOH

The carboxyl group

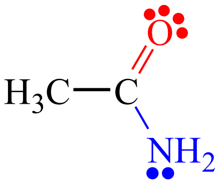
Formic acid  or HCO_2H or HCOOH

Acetic acid  or CH_3CO_2H or CH_3COOH

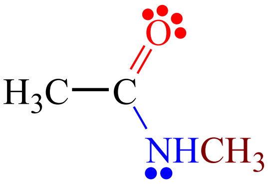
Benzoic acid  or $C_6H_5CO_2H$ or C_6H_5COOH

2.11B AMIDES

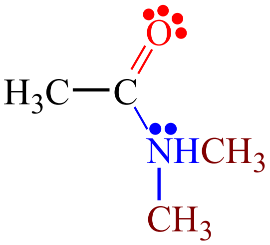
1. Amides have the formulas $RCONH_2$, RCONHR', or RCONR'R":



Acetamide



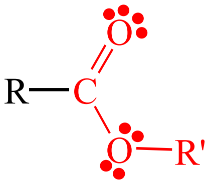
***N*-Methylacetamide**



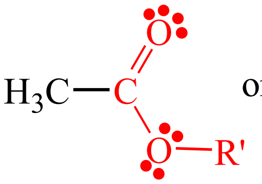
***N,N*-Dimethylacetamide**

2.11C ESTERS

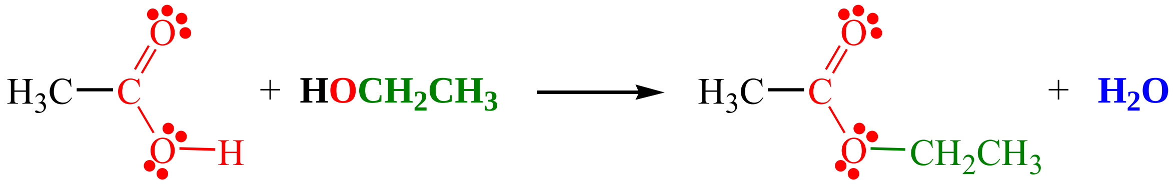
1. Esters have the general formula RCO_2R' (or RCOOR'):

 or RCO_2R' or RCOOR'

General formula for an ester

 or $CH_3CO_2CH_2CH_3$ or $CH_3COOCH_2CH_3$

An specific ester called ethyl acetate



Acetic acid Ethyl alcohol Ethyl acetate

2.12 NITRILES

1. The carbon and the nitrogen of a nitrile are *sp* hybridized.
   1) In IUPAC systematic nonmenclature, acyclic nitriles are named by adding the suffix ***nitrile*** to the name of the corresponding hydrocarbon.

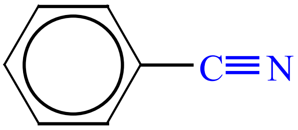
$\overset{2}{H_3C}-\overset{1}{C}\equiv N$
Ethanenitrile (acetonitrile)

$H_3\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}-\overset{1}{C}\equiv N$
Butanenitrile (butyronitrile)

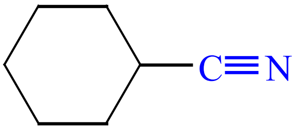
$H_2\overset{3}{C}=\overset{2}{C}H\text{-}\overset{1}{C}\equiv N$
Propenenitrile (acrylonitrile)

$H_2\overset{5}{C}{:}\overset{4}{H}CH_2\overset{3}{C}H_2\overset{2}{C}-\overset{1}{C}\equiv N$
4-Pentenenitrile

   2) Cyclic nitriles are named by adding the suffix ***carbonitrile*** to the name of the ring system to which the –CN group is attached.



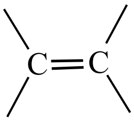
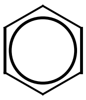
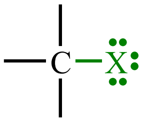
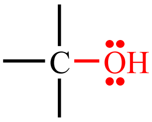
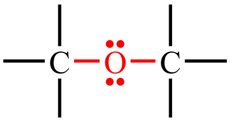
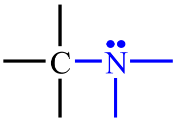
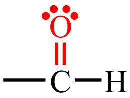
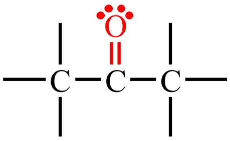
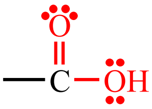
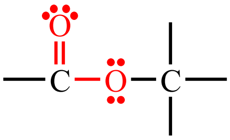
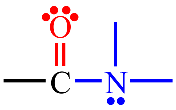
Benzenecarbonitrile (benzonitrile)



Cyclohexanecarbonitrile

2.13 SUMMARY OF IMPORTANT FAMILIES OF ORGANIC COMPOUNDS

Table 2.3 Important Families of Organic Compounds

Family	Specific example	IUPAC name	Common name	General formula	Functional group
Alkane	CH_3CH_3	Ethane	Ethane	RH	C–H and C–C bond
Alkene	$CH_2{=}CH_2$	Ethane	Ethylene	$RCH{=}CH_2$ $RCH{=}CHR$ $R_2C{=}CHR$ $R_2C{=}CR_2$	
Alkyne	$HC{\equiv}CH$	Ethyne	Acetylene	$HC{\equiv}CR$ $RC{\equiv}CR$	$-C{\equiv}C-$
Aromatic		Benzene	Benzene	ArH	Aromatic ring
Haloalkane	CH_3CH_2Cl	Chloroethane	Ethyl chloride	RX	
Alcohol	CH_3CH_2OH	Ethanol	Ethyl alcohol	ROH	
Ether	CH_3OCH_3	Methoxy-methane	Dimethyl ether	ROR	
Amine	CH_3NH_2	Methanamine	Methylamine	RNH_2 R_2NH R_3N	
Aldehyde	$CH_3\overset{\overset{O}{\Vert}}{C}H$	Ethanal	Acetaldehyde	$R\overset{\overset{O}{\Vert}}{C}H$	
Ketone	$CH_3\overset{\overset{O}{\Vert}}{C}CH_3$	Propanone	Acetone	$R\overset{\overset{O}{\Vert}}{C}R'$	
Carboxylic acid	$CH_3\overset{\overset{O}{\Vert}}{C}OH$	Ethanoic acid	Acetic acid	$R\overset{\overset{O}{\Vert}}{C}OH$	
Ester	$CH_3\overset{\overset{O}{\Vert}}{C}OCH_3$	Methyl ethanoate	Methyl acetate	$R\overset{\overset{O}{\Vert}}{C}OR'$	
Amide	$CH_3\overset{\overset{O}{\Vert}}{C}NH_2$	Ethanamide	Acetamide	CH_3CONH_2 CH_3CONHR' $CH_3CONR'R''$	
Nitrile	$H_3CC{\equiv}N{:}$	Ethanenitrile	Acetonitrile	RCN	$-C{\equiv}N{:}$

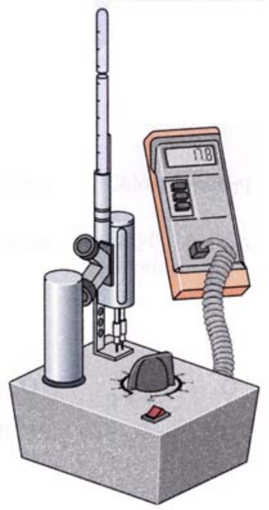
2.14 PHYSICAL PROPERTIES AND MOLECULAR STRUCTURE

1. Physical properties are important in the identification of known compounds.
2. Successful isolation of a new compound obtained in a synthesis depends on making reasonably accurate estimates of the physical properties of its melting point, boiling point, and solubilities.

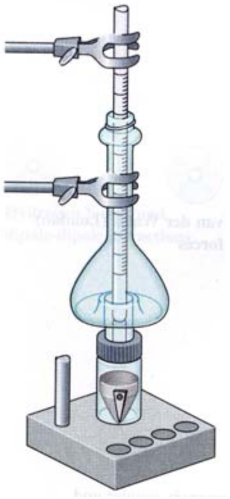
Table 2.4 Physical Properties of Representative Compounds

Compound	Structure	mp (°C)	bp (°C) (1 atm)
Methane	CH_4	-182.6	-162
Ethane	CH_3CH_3	-183	-88.2
Ethene	$CH_2{=}CH_2$	-169	-102
Ethyne	$HC{\equiv}CH$	-82	-84 subl[a]
Chloromethane	CH_3Cl	-97	-23.7
Chloroethane	CH_3CH_2Cl	-138.7	13.1
Ethyl alcohol	CH_3CH_2OH	-115	78.5
Acetaldehyde	CH_3CHO	-121	20
Acetic acid	CH_3CO_2H	16.6	118
Sodium acetate	CH_3CO_2Na	324	dec[a]
Ethylamine	$CH_3CH_2NH_2$	-80	17
Diethyl ether	$(CH_3CH_2)_2O$	-116	34.6
Ethyl acetate	$CH_3CO_2CH_2CH_3$	-84	77

[a] In this table dec = decomposes and subl = sublimes.



An instrument used to measure melting point.



A microscale distillation apparatus.

2.14A ION-ION FORCES

1. The strong electrostatic lattice forces in ionic compounds give them **high melting points**.
2. The **boiling points** of ionic compounds are **higher** still, so high that most ionic organic compounds decompose before they boil.

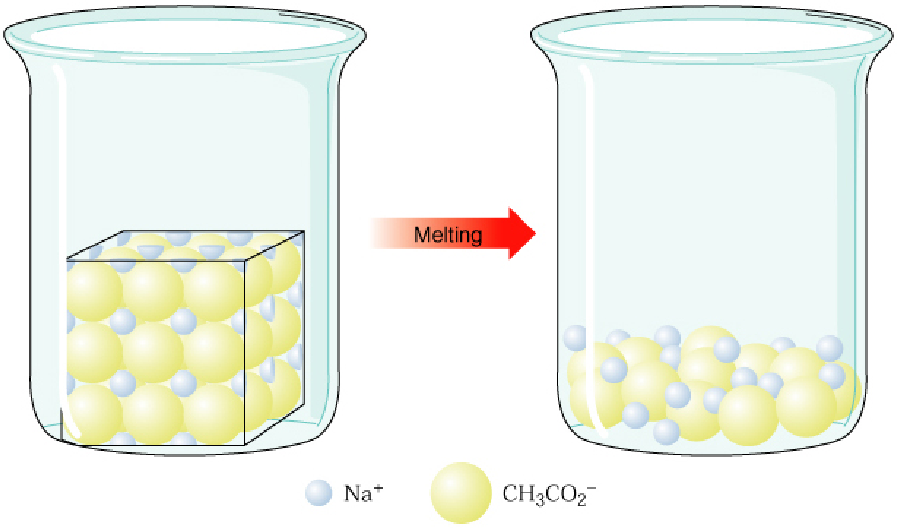


Figure 2.6 The melting of sodium acetate.

2.14B DIPOLE-DIPOLE FORCES

1. **Dipole-dipole** attractions between the molecules of a **polar** compound:

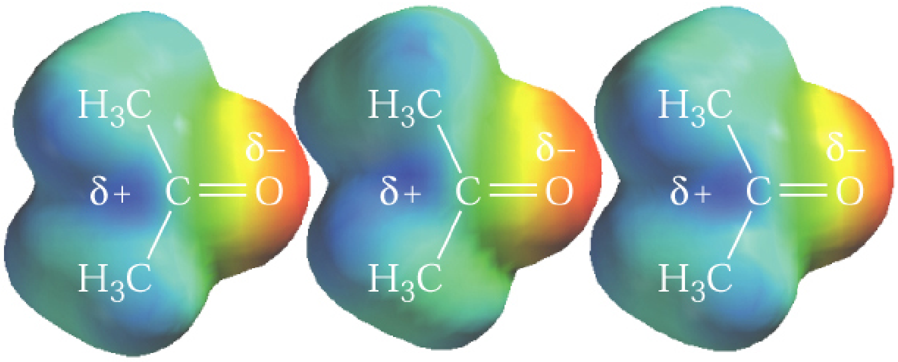
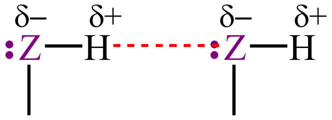


Figure 2.7 Electrostatic potential models for acetone molecules that show how acetone molecules might align according to attractions of their partially positive regions and partially negative regions (dipole-dipole interactions).

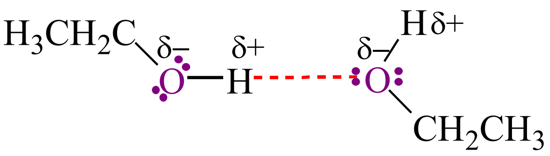
2.14C HYDROGEN BONDS

1. **Hydrogen bond:** the strong **dipole-dipole attractions** between **hydrogen** atoms bonded to small, strongly **electronegative** atoms (O, N, or F) and **nonbonding electron pairs** on other electronegative atoms.
   1) Bond dissociation energy of about 4-38 KJ mol^{-1} (0.96-9.08 Kcal mol^{-1}).
   2) H-bond is weaker than an ordinary covalent bond; much stronger than the dipole-dipole interactions.



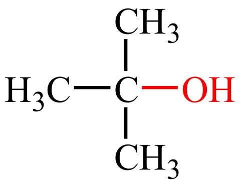
A hydrogen bond (shown by red dots)

*Z is a strongly **electronegative** element, usually oxygen, nitrogen, or fluorine.*



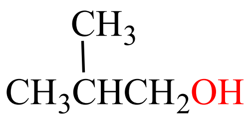
The dotted bond is a hydrogen bond. Strong hydrogen bond is limited to molecules having a hydrogen atom attached to an O, N, or F atom

2. **Hydrogen bonding** accounts for the much higher boiling point (78.5 °C) of ethanol than that of dimethyl ether (–24.9 °C).
3. A factor (in addition to **polarity** and **hydrogen bonding**) that affects the melting point of many organic compounds is the **compactness** and **rigidity** of their individual molecules.

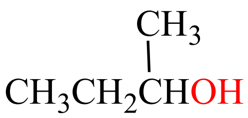


***tert*-Butyl alcohol (mp 25 °C)**

Butyl alcohol (mp –90 °C)



Isobutyl alcohol (mp –108 °C)



***sec*-Butyl alcohol (mp –114 °C)**

2.14D VAN DER WAALS FORCES

1. **van der Waals Forces** (or **London forces** or **dispersion forces**):
   1) The attractive intermolecular forces between the molecules are responsible for the formation of a liquid and a solid of a nonionic, nonpolar substance.
   2) The average distribution of charge in a nonpolar molecule over a period of time is uniform.
   3) At any given instant, ***because electrons move***, the electrons and therefore the **charge** may not be uniformly distributed ⇒ a ***small temporary dipole will occur***.
   4) This temporary dipole in one molecule can induce **opposite** (attractive) dipoles in surrounding molecules.

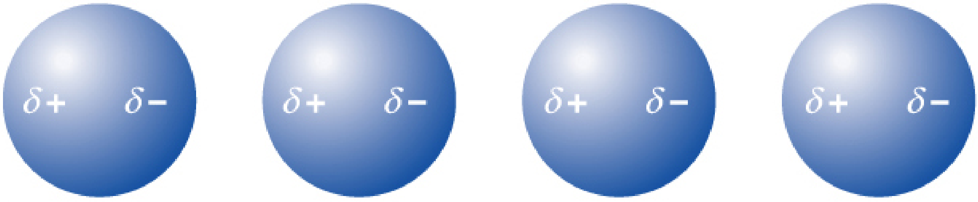


Figure 2.8 **Temporary dipoles and induced dipoles in nonpolar molecules resulting from a nonuniform distribution of electrons at a given instant.**

   5) These temporary dipoles change constantly, but the net result of their existence is to produce attractive forces between nonpolar molecules.

2. **Polarizability:**
   1) The ***ability of the electrons to respond to a changing electric field***.
   2) It determines the magnitude of van der Waals forces.
   3) Relative polarizability depends on how loosely or tightly the electrons are held.
   4) Polarizability increases in the order F < Cl < Br < I.
   5) Atoms with unshared pairs are generally more polarizable than those with only bonding pairs.
   6) Except for the molecules where strong hydrogen bonds are possible, van der Waals forces are far more important than dipole-dipole interactions.

3. The ***boiling point*** of a liquid is the temperature at which the vapor pressure of the liquid equals the pressure of the atmosphere above it.

1) Boiling points of liquids are ***pressure dependent***.
2) The normal bp given for a liquid is its bp at 1 atm (760 torr).
3) The intermolecular van der Waals attractions increase as the size of the molecule increases because the surface areas of heavier molecules are usually much greater.
4) For example: the bp of methane (–162 °C), ethane (–88.2 °C), and decane (174 °C) becomes higher as the molecules grows larger.

Table 2.5 Attractive Energies in Simple Covalent Compounds

Molecule	Dipole moment (D)	Attractive energies (kJ mol^{-1}) Dipole-Dipole	Attractive energies (kJ mol^{-1}) van der Waals	Melting point (°C)	Boiling point (°C)
H_2O	1.85	36[a]	88	0	100
NH_3	1.47	14[a]	15	–78	–33
HCl	1.08	3[a]	17	–115	–85
HBr	0.80	0.8	22	–88	–67
HI	0.42	0.03	28	–51	–35

[a] These dipole-dipole attractions are called hydrogen bonds.

4. **Fluorocarbons** have extraordinarily low boiling points when compared to hydrocarbons of the same molecular weight.

1) 1,1,1,2,2,3,3,4,4,5,5,5-Dodecafluoropentane (C_5F_{12}, m.w. 288.03, bp 28.85 °C) has a slightly lower bp than pentane (C_5H_{12}, m.w. 72.15, bp 36.07 °C).
2) Fluorine atom has very low polarizability resulting in very small van der Waals forces.
3) Teflon has self-lubricating properties which are utilized in making "**nonstick**" frying pans and lightweight bearings.

2.14E SOLUBILITIES

1. **Solubility**

   1) The energy required to overcome lattice energies and intermolecular or interionic attractions for the dissolution of a solid in a liquid comes from the formation of new attractions between solute and solvent.
   2) The dissolution of an ionic substance: **hydrating** or **solvating** the ions.
   3) Water molecules, by virtue of their great polarity and their very small, compact shape, can very effectively surround the individual ions as they freed from the crystal surface.
   4) Because water is highly **polar** and is capable of forming strong **H-bonds**, the ***dipole-ion*** attractive forces are also large.

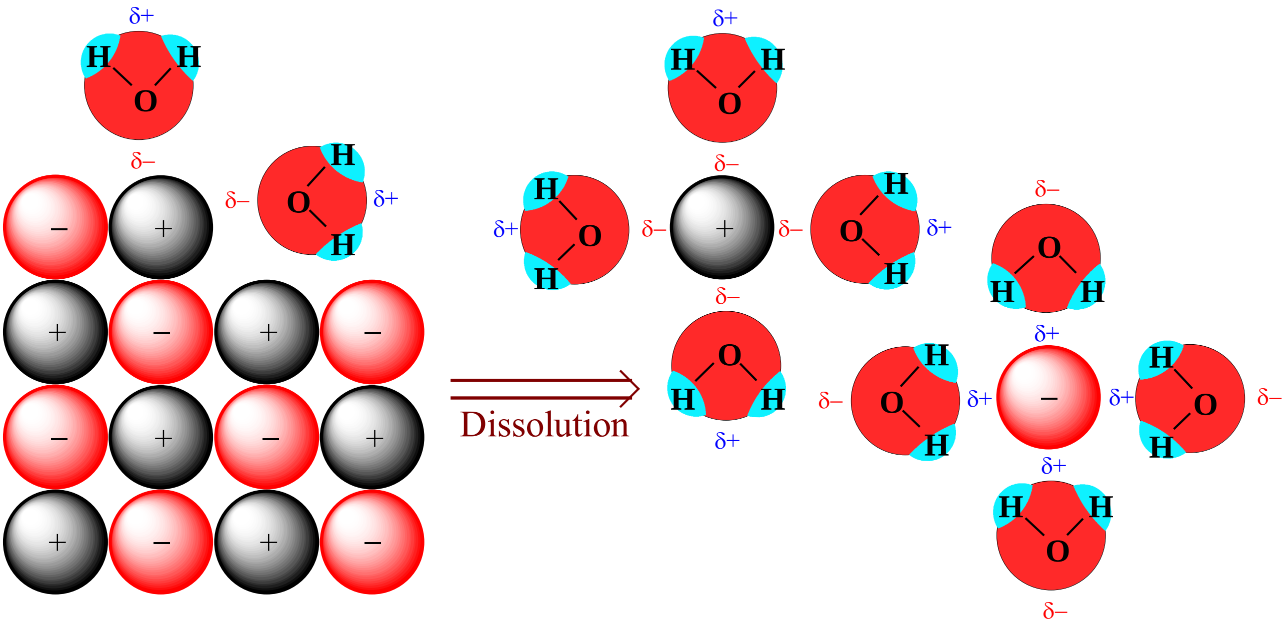


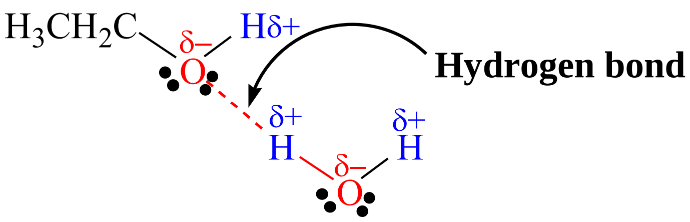
Figure 2.9 **The dissolution of an ionic solid in water, showing the hydration of positive and negative ions by the very polar water molecules. The ions become surrounded by water molecules in all three dimensions, not just the two shown here.**

2. "***Like dissolves like***"

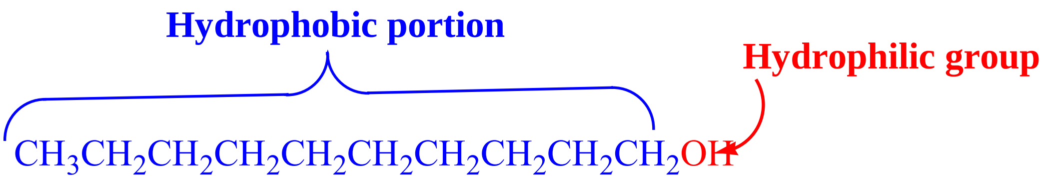
   1) Polar and ionic compounds tend to dissolve in polar solvents.
   2) Polar liquids are generally miscible with each other.
   3) Nonpolar solids are usually soluble in nonpolar solvents.

4) Nonpolar solids are insoluble in polar solvents.
5) Nonpolar liquids are usually mutually miscible.
6) Nonpolar liquids and polar liquids do not mix.

3. Methanol (ethanol, and propanol) and water are miscible in all proportions.



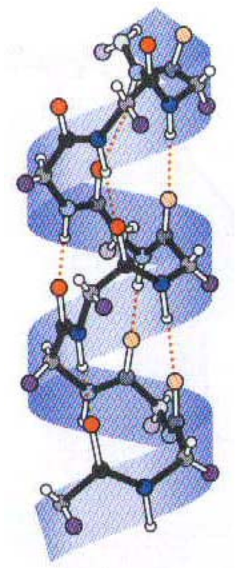
1) Alcohol with long carbon chain is much less soluble in water.
2) The long carbon chain of decyl alcohol is **hydrophobic** (hydro, water; ***phobic***, fearing or avoiding — "water avoiding".
3) The OH group is **hydrophilic** (***philic***, loving or seeking — "water seeking".



Decyl alcohol

2.14F Guidelines for Water Solubilities

1. Water **soluble**: at least 3 g of the organic compound dissolves in 100 mL of water.
   1) Compounds containing one hydrophilic group: 1-3 carbons are water soluble; 4-5 carbons are borderline; 6 carbons or more are insoluble.

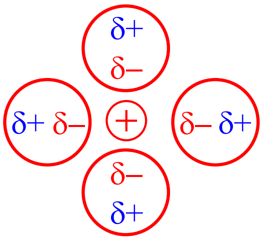
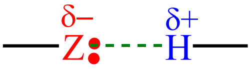
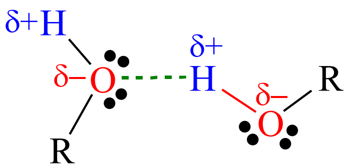
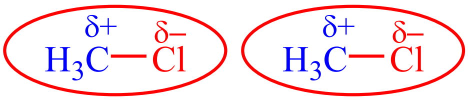


2.14G Intermolecular Forces in Biochemistry

Hydrogen bonding (red dotted lines) in the α-helix structure of proteins.

2.15 SUMMARY OF ATTRACTIVE ELECTRIC FORCES

Table 2.6 Attractive Electric Forces

Electric Force	Relative Strength	Type	Example
Cation-anion (in a crystal)	Very strong	⊕ ⊖	Lithium fluoride crystal lattice
Covalent bonds	Strong (140-523 kJ mol^{-1})	Shared electron pairs	H–H (435 kJ mol^{-1}) CH_3–CH_3 (370 kJ mol^{-1}) I–I (150 kJ mol^{-1})
Ion-dipole	Moderate		Na^+ in water (see Fig. 2.9)
Dipole-dipole (including hydrogen bonds)	Moderate to weak (4-38 kJ mol^{-1})		 and 
van der Waals	Variable	Transient dipole	Interactions between methane molecules

2.16 INFRARED SPECTROSCOPY: AN INSTRUMENTAL METHOD

2.16A An Infrared spectrometer:

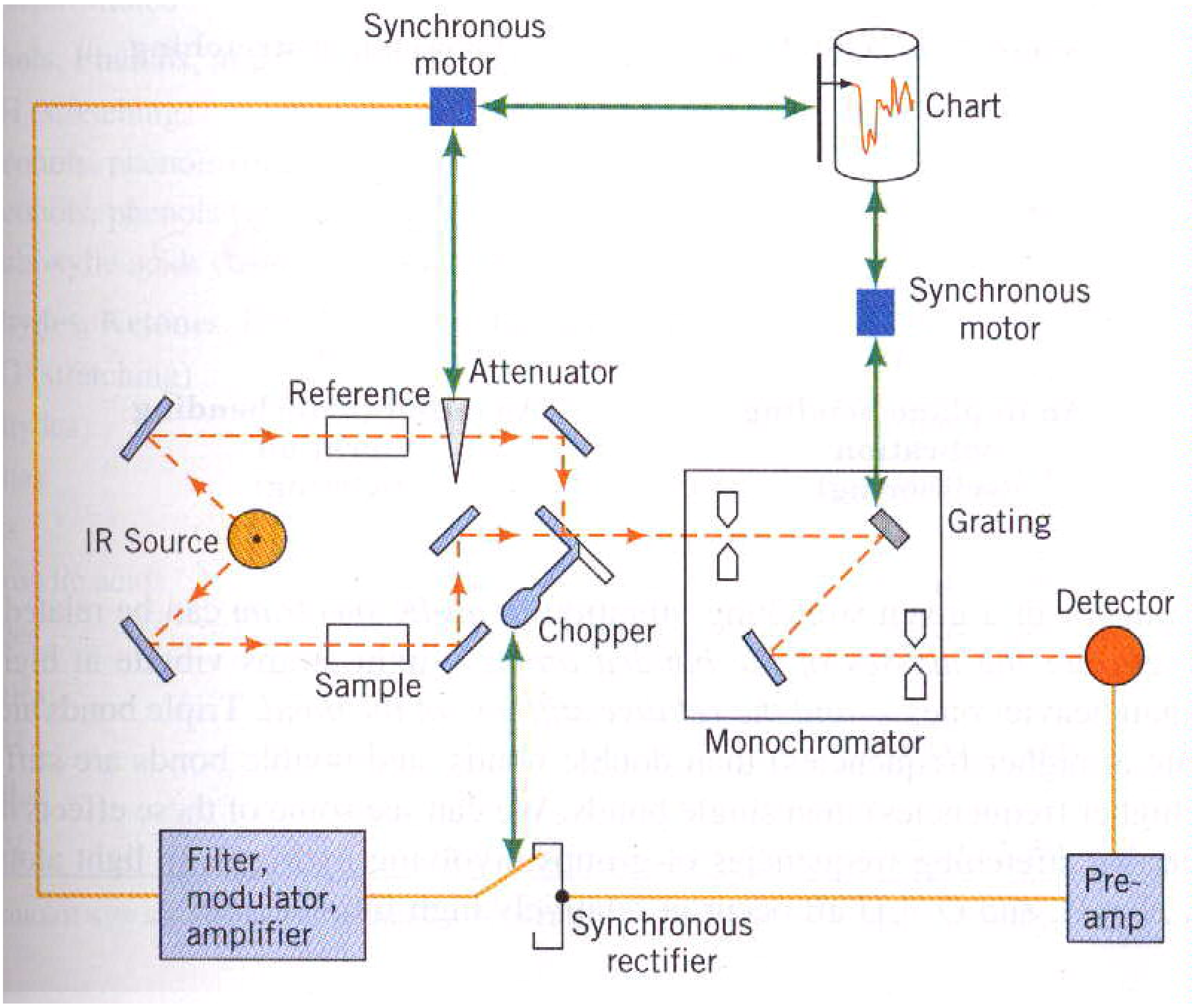
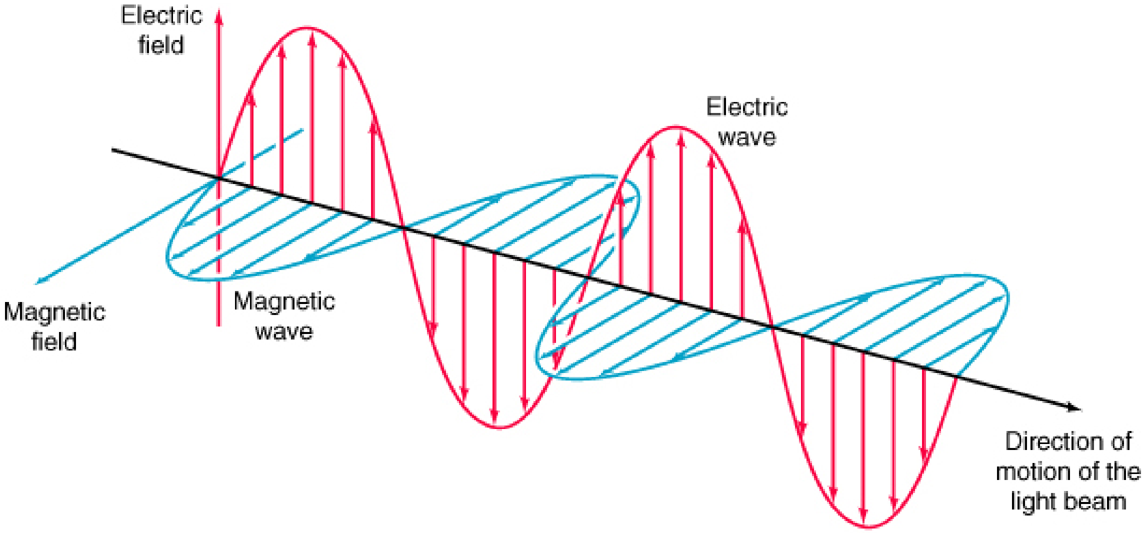


Figure 2.10 **Diagram of a double-beam infrared spectrometer. [From Skoog D. A.; Holler, F. J.; Kieman, T. A. *principles of instrumental analysis*, 5th ed., Saunders: New York, 1998; p 398.].**

1. **RADIATION SOURCE:**
2. **SAMPLING AREA:**
3. **PHOTOMETER:**
4. **MONOCHROMATOR:**
5. **DETECTOR (THERMOCOUPLE):**



The oscillating electric and magnetic fields of a beam of ordinary light in one plane. The waves depicted here occur in all possible planes in ordinary light.

2.16B Theory:

1. **Wavenumber** ($\bar{\nu}$):

$$\bar{\nu}\ (\text{cm}^{-1}) = \frac{1}{\lambda\ (\text{cm})} \qquad \nu\ (\text{Hz}) = \bar{\nu}\, c\ (\text{cm}) = \frac{c\ (\text{cm/sec})}{\lambda\ (\text{cm})}$$

$$\text{cm}^{-1} = \frac{1}{(\mu)} \times 10{,}000 \quad \text{and} \quad \mu = \frac{1}{(\text{cm}^{-1})} \times 10{,}000$$

* the wavenumbers ($\bar{\nu}$) are often called "frequencies".

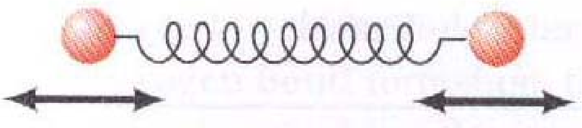
2. **THE MODES OF VIBRATION AND BENDING:**

Degrees of freedom:

Nonlinear molecules:	3N–6	vibrational degrees of freedom
linear molecules:	3N–5	(fundamental vibrations)

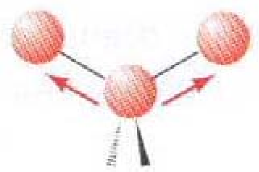
* Fundamental vibrations involve no change in the center of gravity of the molecule.

3. **"*Bond vibration*":**

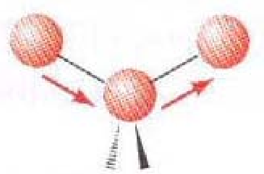


A stretching vibration

4. “***Stretching***”:



Symmetric stretching



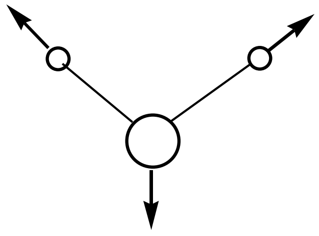
Asymmetric stretching

5. “***Bending***”:

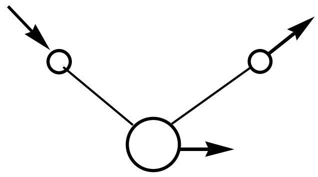
Symmetric bending

Asymmetric bending

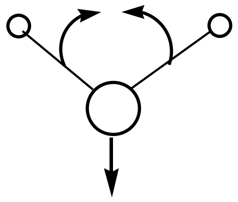
6. H_2O: 3 fundamental vibrational modes $3N - 3 - 3 = 3$



Symmetrical stretching
(ν_s OH)
3652 cm^{-1} (2.74 μm)



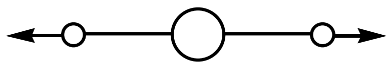
Asymmetrical stretching
(ν_{as} OH)
3756 cm^{-1} (2.66 μm)



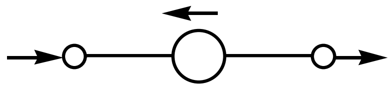
Scissoring
(ν_s HOH)
1596 cm^{-1} (6.27 μm)

coupled stretching

7. CO_2: 4 fundamental vibrational modes $3N - 3 - 2 = 4$



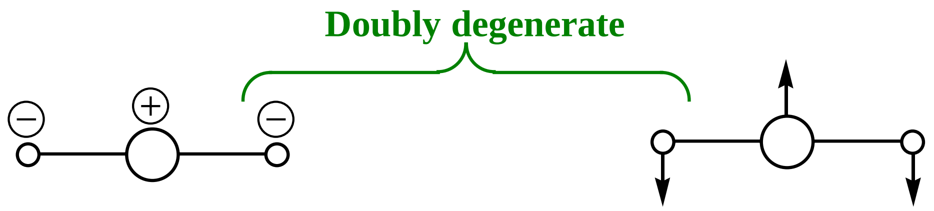
Symmetrical stretching
(ν_s CO)
1340 cm^{-1} (7.46 μm)



Asymmetrical stretching
(ν_{as} CO)
2350 cm^{-1} (4.26 μm)

coupled stretching

normal C=O 1715 cm^{-1}



Scissoring (bending)
(δ_s CO)
666 cm^{-1} (15.0 μm)

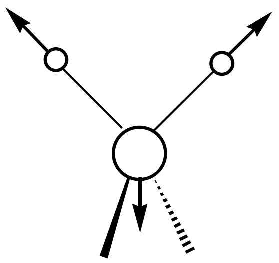
Scissoring (bending)
(δ_s CO)
666 cm^{-1} (15.0 μm)

resolved components of bending motion

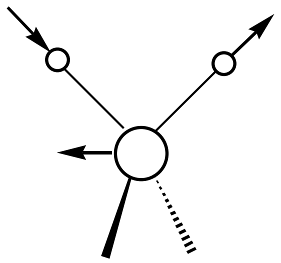
⊕ and ⊖ indicate movement perpendicular to the plane of the page

8. AX_2:

Stretching Vibrations

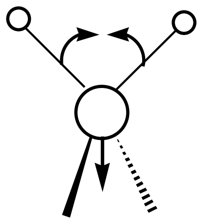


Symmetrical stretching
(ν_s CH_2)

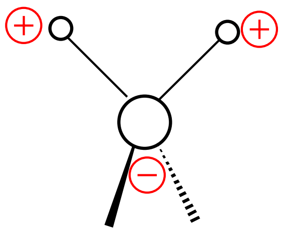


Asymmetrical stretching
(ν_{as} CH_2)

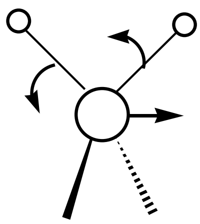
Bending Vibrations



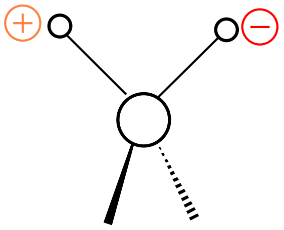
In-plane bending or scissoring
(δ_s CH_2)



Out-of-plane bending or wagging
(ω CH_2)



In-plane bending or rocking
(ρ_s CH_2)



Out-of-plane bending or twisting
(τ CH_2)

9. Number of fundamental vibrations observed in IR will be influenced:

(1) Overtones
(2) Combination tones
$\Rightarrow$ increase the number of bands

(3) Fall outside 2.5-15 μm region
Too weak to be observed
Two peaks that are too close
Degenerate band
Lack of dipole change
$\Rightarrow$ reduce the number of bands

10. Calculation of approximate stretching frequencies:

$$\bar{\nu} = \frac{1}{2\pi c}\sqrt{\frac{K}{\mu}} \quad \Rightarrow \quad \nu\,(\text{cm}^{-1}) = 4.12\sqrt{\frac{K}{\mu}}$$

$\bar{\nu}$ = frequency in cm^{-1}

c = velocity of light = 3×10^{10} cm/sec

$\mu = \frac{m_1 m_2}{m_1 + m_2}$ masses of atoms in grams or $\frac{M_1 M_2}{(M_1 + M_2)(6.02 \times 10^{23})}$ masses of atoms in amu

$\mu = \frac{M_1 M_2}{M_1 + M_2}$ where M_1 and M_2 are atomic weights

K = force constant in dynes/cm

$K = 5 \times 10^5$ dynes/cm (single)
$= 10 \times 10^5$ dynes/cm (double)
$= 15 \times 10^5$ dynes/cm (triple)

(1) C=C bond:

$$\bar{\nu} = 4.12\sqrt{\frac{K}{\mu}} \qquad K = 10 \times 10^5 \text{ dynes/cm} \qquad \mu = \frac{M_C M_C}{M_C + M_C} = \frac{(12)(12)}{12+12} = 6$$

$$\bar{\nu} = 4.12\sqrt{\frac{10 \times 10^5}{6}} = 1682 \text{ cm}^{-1} \text{ (calculated)} \qquad \bar{\nu} = 1650 \text{ cm}^{-1} \text{ (experimental)}$$

(2)

C–H bond

$$\bar{\nu} = 4.12\sqrt{\frac{K}{\mu}}$$

K= 5 x 10^5 dynes/cm

$$\mu = \frac{M_C M_H}{M_C + M_H} = \frac{(12)(1)}{12+1} = 0.923$$

$$\bar{\nu} = 4.12\sqrt{\frac{5 \text{ x } 10^5}{0.923}} = 3032 \text{ cm}^{-1} \text{ (calculated)};$$

$\bar{\nu}$ = 3000 cm^{-1} (experimental)

C–D bond

$$\bar{\nu} = 4.12\sqrt{\frac{K}{\mu}}$$

K= 5 x 10^5 dynes/cm

$$\mu = \frac{M_C M_D}{M_C + M_D} = \frac{(12)(2)}{12+2} = 1.71$$

$$\bar{\nu} = 4.12\sqrt{\frac{5 \text{ x } 10^5}{1.71}} = 2228 \text{ cm}^{-1} \text{ (calculated)};$$

$\bar{\nu}$ = 2206 cm^{-1} (experimental)

(3)

C≡C	C=C	C—C
2150 cm^{-1}	1650 cm^{-1}	1200 cm^{-1}

← increasing K

C—H	C—C	C—O	C—Cl	C—Br	C—I
3000 cm^{-1}	1200 cm^{-1}	1100 cm^{-1}	800 cm^{-1}	550 cm^{-1}	~500 cm^{-1}

increasing μ →

(4) Hybridization affects the force constant K:

sp	*sp*^{2}	*sp*^{3}
≡C—H	=C—H	—C—H
3300 cm^{-1}	3100 cm^{-1}	2900 cm^{-1}

(5) K increases from left to the right across the periodic table:

C–H: 3040 cm^{-1} F–H: 4138 cm^{-1}

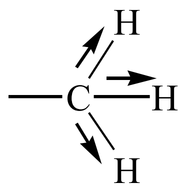
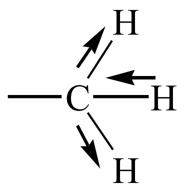
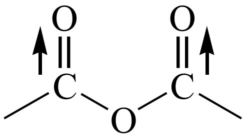
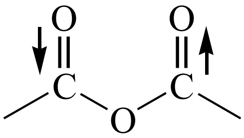
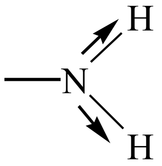
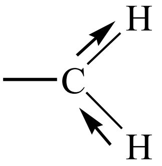
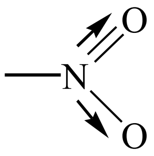
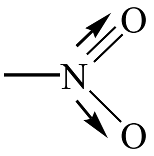
(6) Bending motions are easier than stretching motions:

C–H stretching: ~ 3000 cm^{-1} C–H bending: ~ 1340 cm^{-1}

2.16C Coupled Interactions:

1. CO_2: symmetrical 1340 cm^{-1} asymmetrical 2350 cm^{-1} normal 1715 cm^{-1}

2.

	Symmetric Stretch	Asymmetric Stretch
Methyl	 ~ 2872 cm^{-1}	 ~ 2962 cm^{-1}
Anhydride	 ~ 1760 cm^{-1}	 ~ 1800 cm^{-1}
Amine	 ~ 3300 cm^{-1}	 ~3400 cm^{-1}
Nitro	 ~ 1350 cm^{-1}	 ~ 1550 cm^{-1}

Asymmetric stretching vibrations occur at higher frequency than symmetric ones.

3.
$$\left\{\begin{array}{lll} H{-}CH_2{-}OH: & \nu_{C-O} & 1034\ \text{cm}^{-1} \\ H_3C{-}CH_2{-}OH: & \nu_{C-O} & 1053\ \text{cm}^{-1} \end{array}\right\} \Longrightarrow \nu_{C-C-O}$$

2.16D HYDROCARBONS:

1. ALKANES:

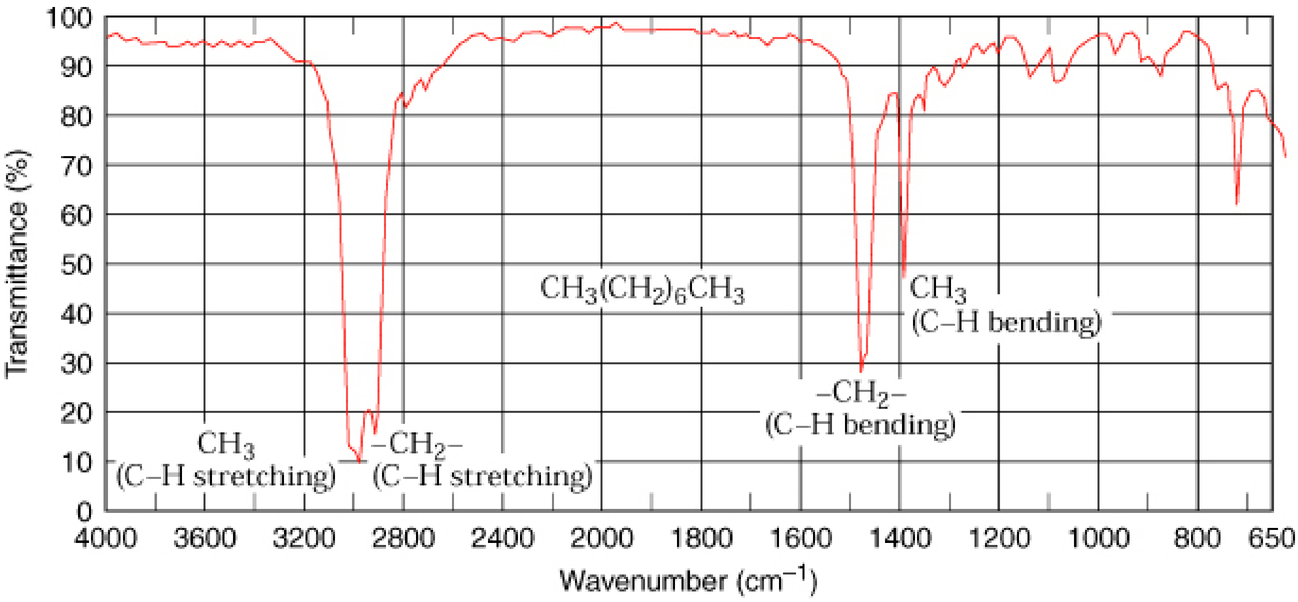


Figure 2.11 The IR spectrum of octane.

2. AROMATIC COMPOUNDS:

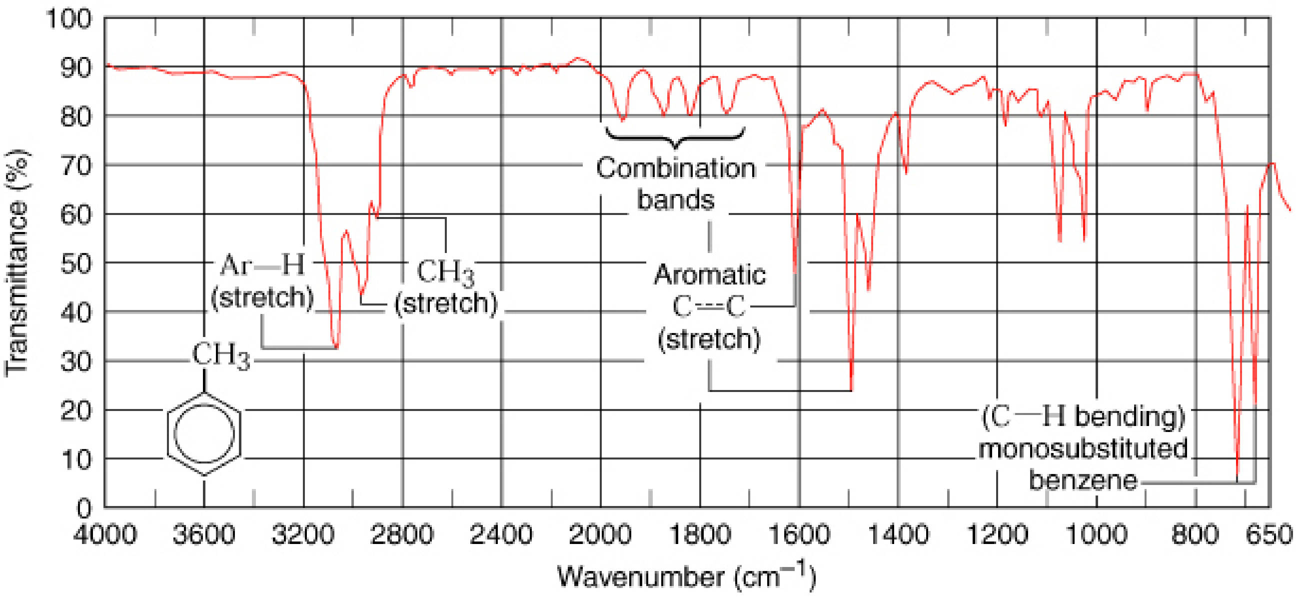


Figure 2.12 The IR spectrum of methylbenzene (toluene).

3. ALKYNES:

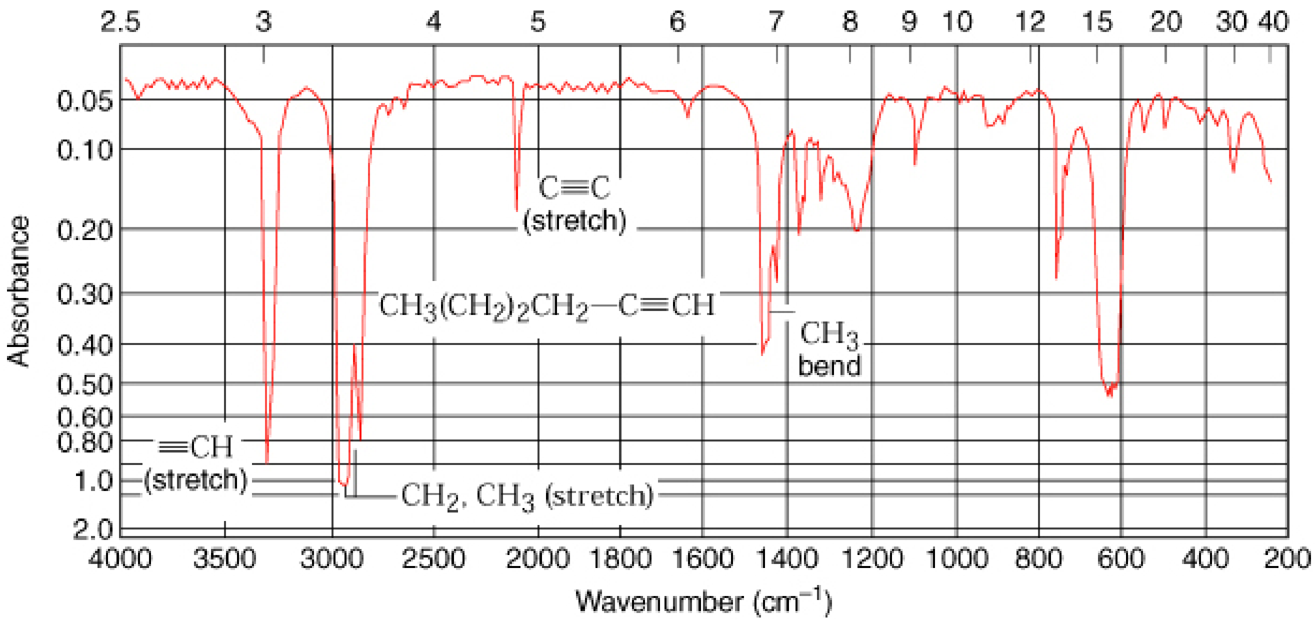


Figure 2.13 The IR spectrum of 1-hexyne.

4. ALKENES:

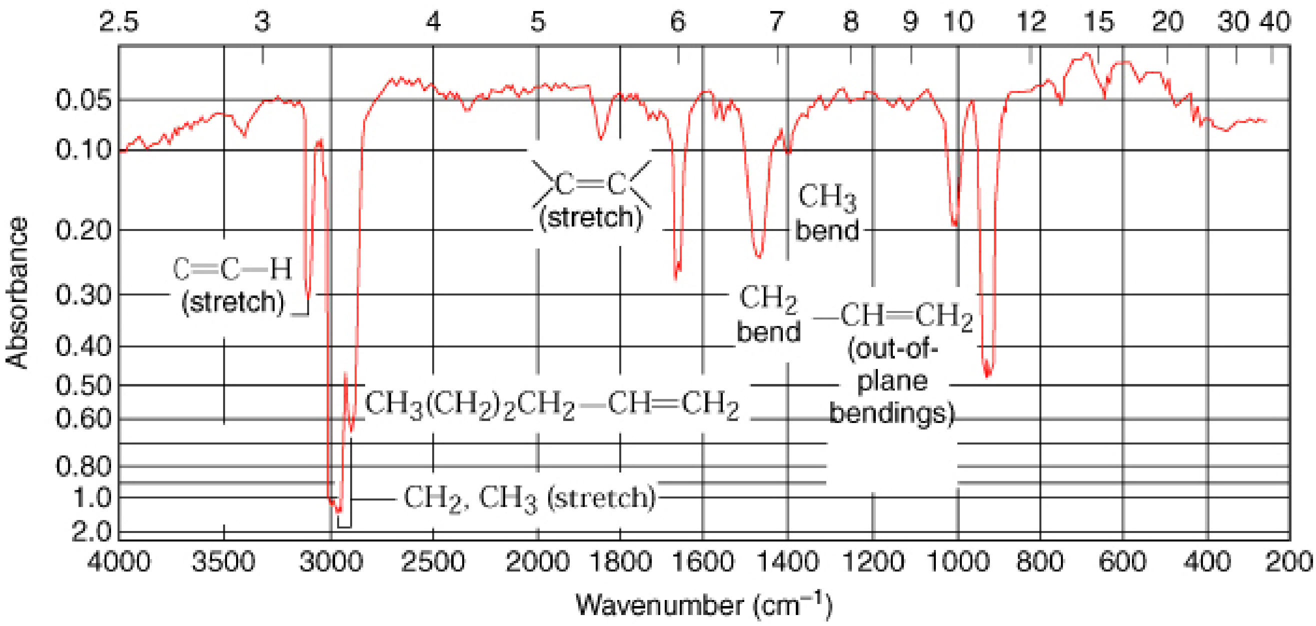


Figure 2.14 The IR spectrum of 1-hexene.

2.16E OTHER FUNCTIONAL GROUPS

1. Shape and intensity of IR peaks:

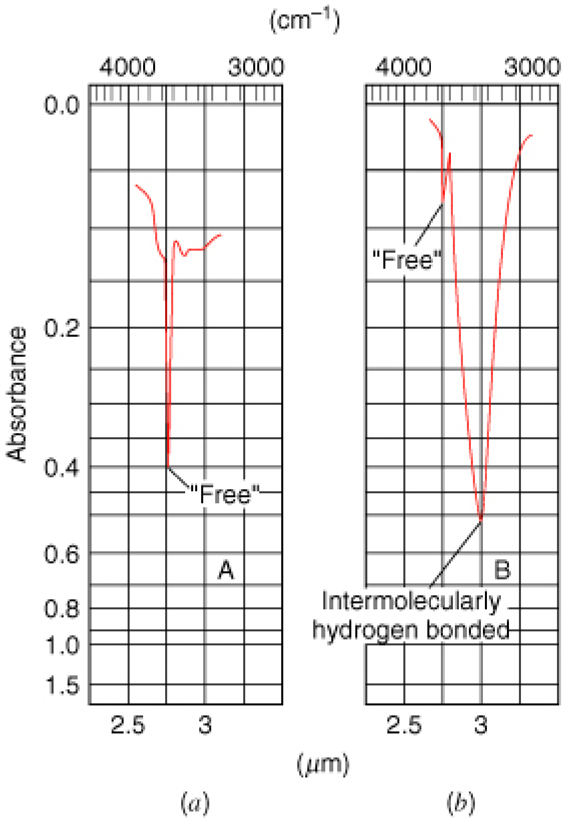


Figure 2.15 The IR spectrum of cyclohexanol .

2. Acids:

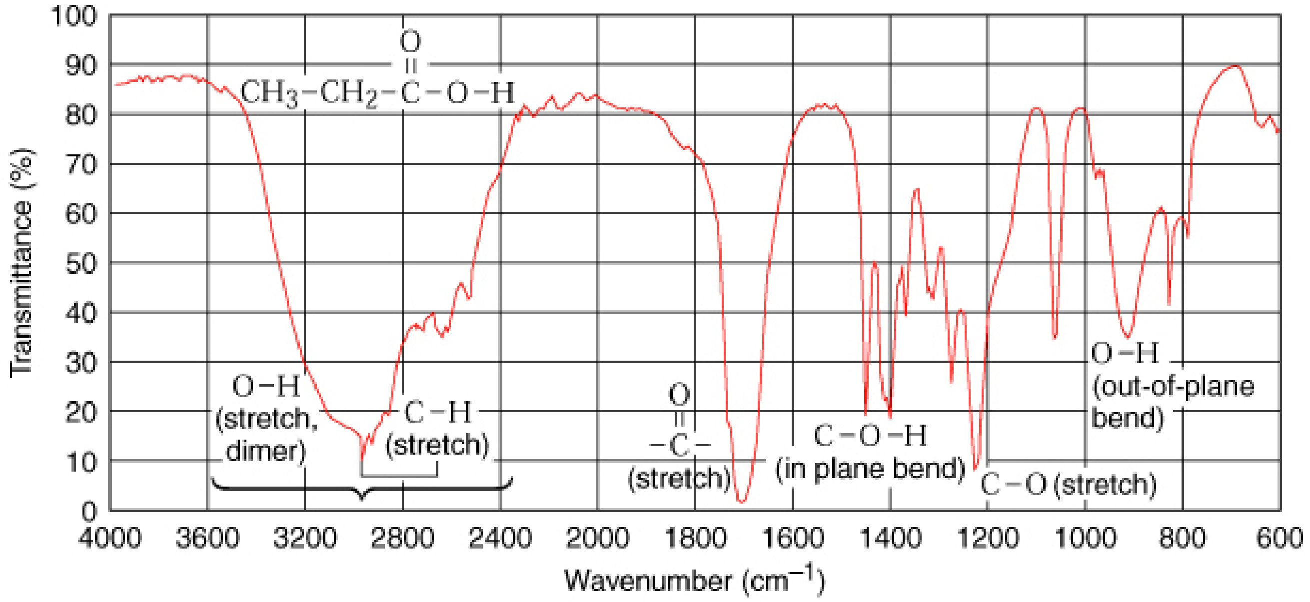


Figure 2.16 The infrared spectrum of propanoic acid.

How To Approach The Analysis of A Spectrum

1. Is a carbonyl group present?

The C=O group gives rise to a strong absorption in the region 1820-1660 cm^{-1} (5.5-6.1 μ). The peak is often the strongest in the spectrum and of medium width. You can't miss it.

2. If C=O is present, check the following types (if absent, go to 3).

ACIDS is OH also present?

– *broad* absorption near 3400-2400 cm^{-1} (usually overlaps C–H)

AMIDES is NH also present?

– medium absorption near 3500 cm^{-1} (2.85 μ)

Sometimes a double peak, with equivalent halves.

ESTERS is C–O also present?

– strong intensity absorptions near 1300-1000 cm^{-1} (7.7-10 μ)

ANHYDRIDES have *two* C=O absorptions near 1810 and 1760 cm^{-1} (5.5 and 5.7 μ)

ALDEHYDES is aldehyde CH present?

– two weak absorptions near 2850 and 2750 cm^{-1} (3.50 and 3.65 μ) on the right-hand side of CH absorptions

KETONES The above 5 choices have been eliminated

3. If C=O is absent

ALCOHOLS Check for OH

PHENOLS – *broad* absorption near 3400-2400 cm^{-1} (2.8-3.0 μ)

– confirm this by finding C–O near 1300-1000 cm^{-1} (7.7-10 μ)

AMINES Check for NH

– medium absorptions(s) near 3500 cm^{-1} (2.85 μ)

ETHERS Check for C–O (and absence of OH) near 1300-1000 cm^{-1} (7.7-10 μ)

4. Double Bonds and/or Aromatic Rings

– C=C is a *weak* absorption near 1650 cm^{-1} (6.1 μ)

– medium to strong absorptions in the region 1650-1450 cm^{-1} (6-7 μ) often imply an aromatic ring

– confirm the above by consulting the CH region; aromatic and vinyl CH occurs to the left of 3000 cm^{-1} (3.33 μ) (aliphatic CH occurs to the right of this value)

5. Triple Bonds

– C≡N is a medium, sharp absorption near 2250 cm^{-1} (4.5 μ)

– C≡C is a weak but sharp absorption near 2150 cm^{-1} (4.65 μ)

Check also for acetylenic CH near 3300 cm^{-1} (3.0 μ)

6. Nitro Groups

– two strong absorptions at 1600 - 1500 cm^{-1} (6.25-6.67 μ) and 1390-1300 cm^{-1} (7.2-7.7 μ)

7. Hydrocarbons

– none of the above are found

– major absorptions are in CH region near 3000 cm^{-1} (3.33 μ)

– very simple spectrum, only other absorptions near 1450 cm^{-1} (6.90 μ) and 1375 cm^{-1} (7.27 μ)

Note: In describing the shifts of absorption peaks or their relative positions, we have used the terms "to the left" and "to the right." This was done to save space when using *both* microns and reciprocal centimeters. The meaning is clear since all spectra are conventionally presented left to right from 4000 cm^{-1} to 600 cm^{-1} or from 2.5 μ to 16 μ. "To the right" avoids saying each time "to lower frequency (cm^{-1}) or to longer wavelength (μ)" which is confusing since cm^{-1} and μ have an inverse relationship; as one goes up, the other goes down.

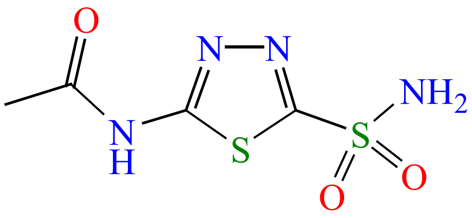
AN INTRODUCTION TO ORGANIC REACTIONS: ACIDS AND BASES

SHUTTLING THE PROTONS

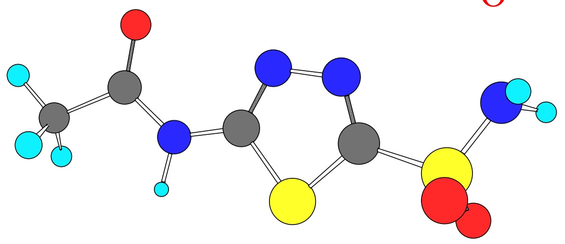
1. **Carbonic anhydrase** regulates the acidity of blood and the physiological conditions relating to blood pH.

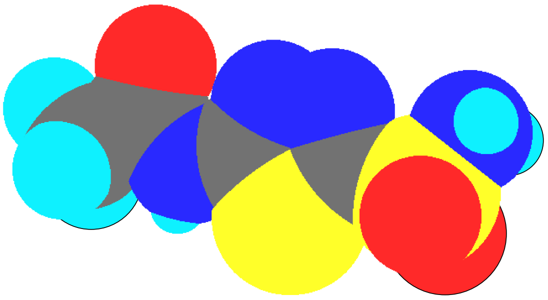
$$HCO_3^- + H^+ \rightleftharpoons H_2CO_3 \xrightleftharpoons{\text{Carbonic anhydrase}} H_2O + CO_2$$

2. The breath rate is influenced by one’s relative blood acidity.
3. **Diamox** (acetazolamide) **inhibits** carbonic anhydrase, and this, in turn, **increases the blood acidity**. The increased blood acidity **stimulates breathing** and thereby decreases the likelihood of **altitude sickness**.



Diamox (acetazolamide)





3.1 REACTIONS AND THEIR MECHANISMS

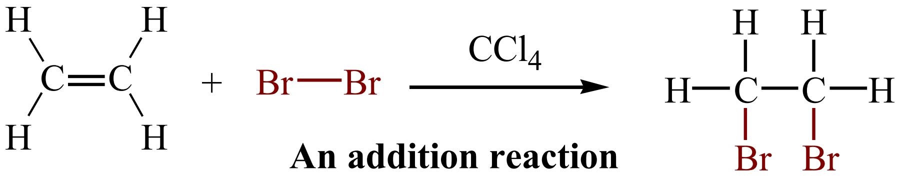
3.1A CATEGORIES OF REACTIONS

1. **Substitution Reactions:**

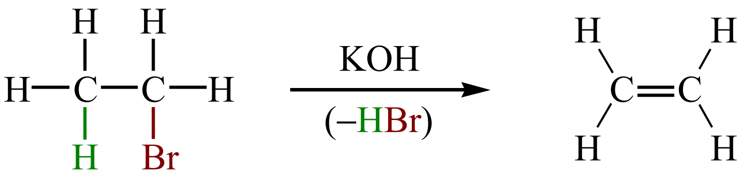
$$H_3C{-}Cl + Na^+\,OH^- \xrightarrow{H_2O} H_3C{-}OH + Na^+\,Cl^-$$

A substitution reaction

2. **Addition Reactions:**

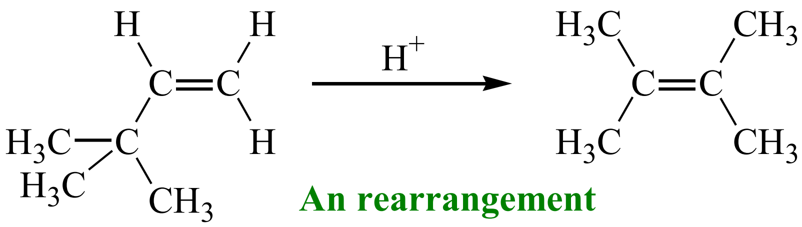


3. **Elimination Reactions:**



An elimination reaction (Dehydrohalogenation)

4. **Rearrangement Reactions:**



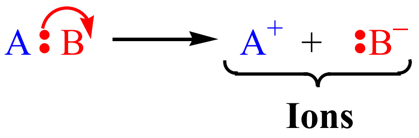
3.1B MECHANISMS OF REACTIONS

1. **Mechanism** explains, on a molecular level, how the reactants become products.
2. **Intermediates** are the chemical species generated between each step in a multistep reaction.
3. A proposed mechanism must be **consistent** with all the **facts** about the reaction and with the **reactivity** of organic compounds.
4. Mechanism helps us organize the seemingly an overwhelmingly complex body of knowledge into an understandable form.

3.1C HOMOLYSIS AND HETEROLYSIS OF COVALENT BONDS

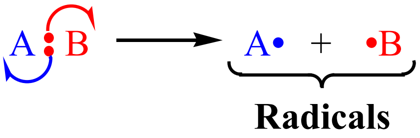
1. **Heterolytic** bond dissociation (**heterolysis**): electronically *unsymmetrical* bond

breaking ⇒ produces **ions**.



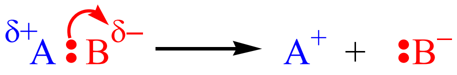
Hydrolytic bond cleavage

2. **Homolytic** bond dissociation (**homolysis**): electronically *symmetrical* bond breaking ⇒ produces **radicals**.

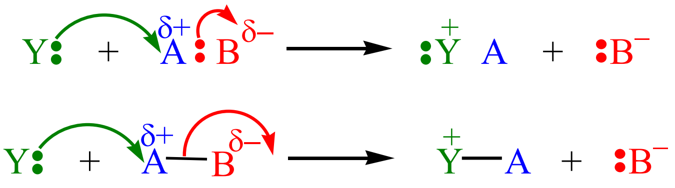


Homolytic bond cleavage

3. **Heterolysis** requires the bond to be **polarized**. ***Heterolysis requires separation of oppositely charged ions***.



4. **Heterolysis** is assisted by a molecule with an **unshared pair**:

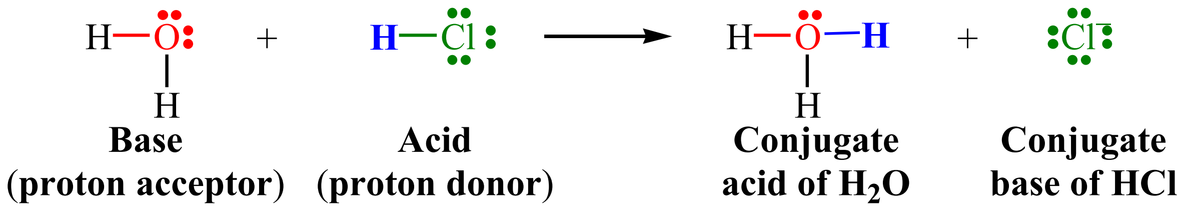


Formation of the new bond furnishes some of the energy required for the heterolysis.

3.2 Acid-Base Reactions

3.2A The Brønsted-Lowry Definition of Acids and Bases

1. **Acid** is a substance that can donate (or lose) a **proton**; **Base** is a substance that can accept (or remove) a **proton**.



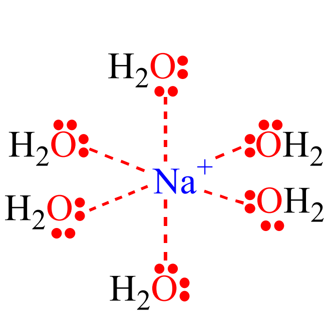
1) Hydrogen chloride, a very strong acid, transfer its proton to water.
2) Water acts as a base and accepts the proton.

2. **Conjugate acid:** the molecule or ion that forms when a base accepts a proton.
3. **Conjugate base:** the molecule or ion that forms when an acid loses its proton.
4. Other strong acids:

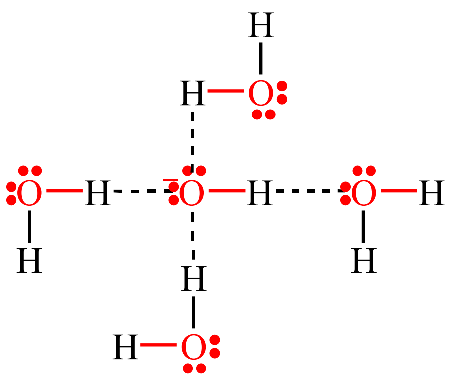
Hydrogen iodide	$HI + H_2O \longrightarrow H_3O^+ + I^-$
Hydrogen bromide	$HBr + H_2O \longrightarrow H_3O^+ + Br^-$
Sulfuric acid	$H_2SO_4 + H_2O \longrightarrow H_3O^+ + HSO_4^-$
	$HSO_4^- + H_2O \longrightarrow H_3O^+ + SO_4^{2-}$ (~10%)

5. **Hydronium** ions and **hydroxide** ions are the strongest acid and base that can exist in aqueous solution in significant amounts.
6. When sodium hydroxide dissolves in water, the result is a solution containing solvated sodium ions and solvated hydroxide ions.

$$Na^+\,OH^-_{(solid)} \longrightarrow Na^+_{(aq)} + HO^-_{(aq)}$$



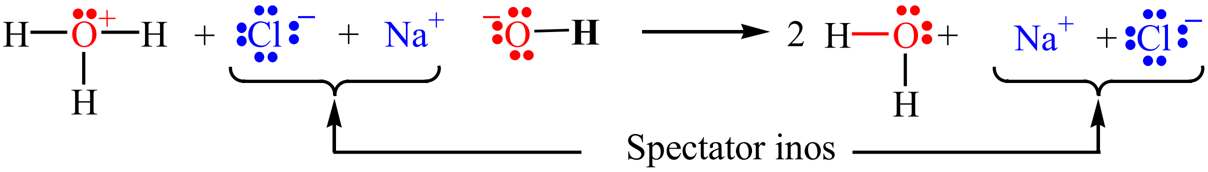
Solvated sodium ion



Solvated hydroxide ion

7. An aqueous **sodium hydroxide** solution is mixed with an aqueous **hydrogen chloride** (hydrochloric acid) solution:

1) ***Total Ionic Reaction***



2) ***Net Reaction***

3) The ***Net Reaction*** of solutions of all aqueous strong acids and bases are mixed:

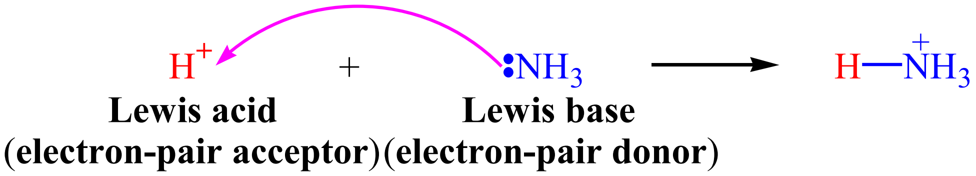
$$H_3O^+ + OH^- \longrightarrow 2\ H_2O$$

3.2B The Lewis Definition of Acids and Bases

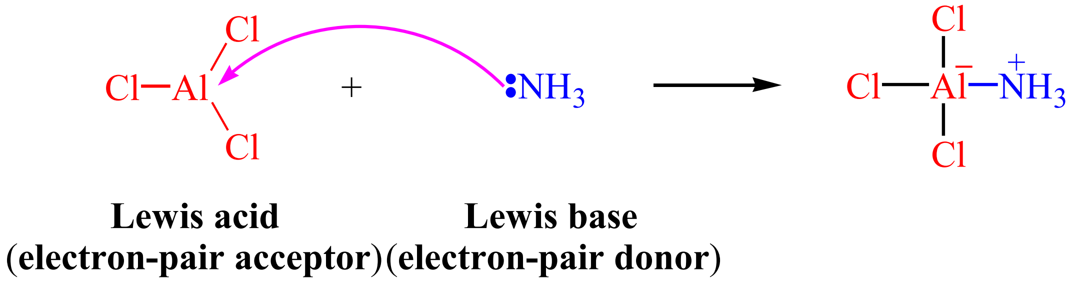
1. **Lewis acid-base** theory: in 1923 proposed by G. N. Lewis (1875~1946; Ph. D. Harvard, 1899; professor, Massachusetts Institute of Technology, 1905-1912; professor, University of California, Berkeley, 1912-1946).

1) **Acid: electron-pair acceptor**

2) **Base: electron-pair donor**

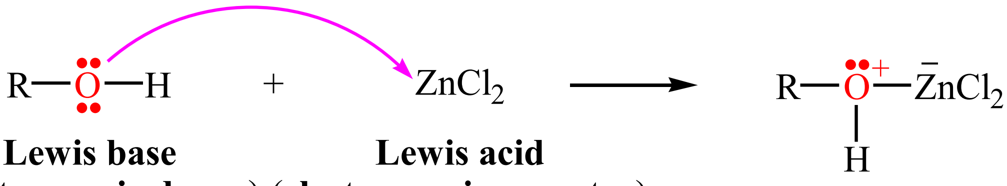


curved arrow shows the donation of the electron-pair of ammonia



3) The central aluminum atom in aluminum chloride is **electron-deficient** because it has only a **sextet** of electrons. Group 3A elements (B, Al, Ga, In, Tl) have only a **sextet** of electrons in their valence shell.

4) Compounds that have atoms with vacant orbitals also can act as Lewis acids.



Lewis base (electron-pair donor) **Lewis acid (electron-pair acceptor)**

Lewis base (electron-pair donor) **Lewis acid (electron-pair acceptor)**

3.2C OPPOSITE CHARGES ATTRACT

1. Reaction of boron trifluoride with ammonia:

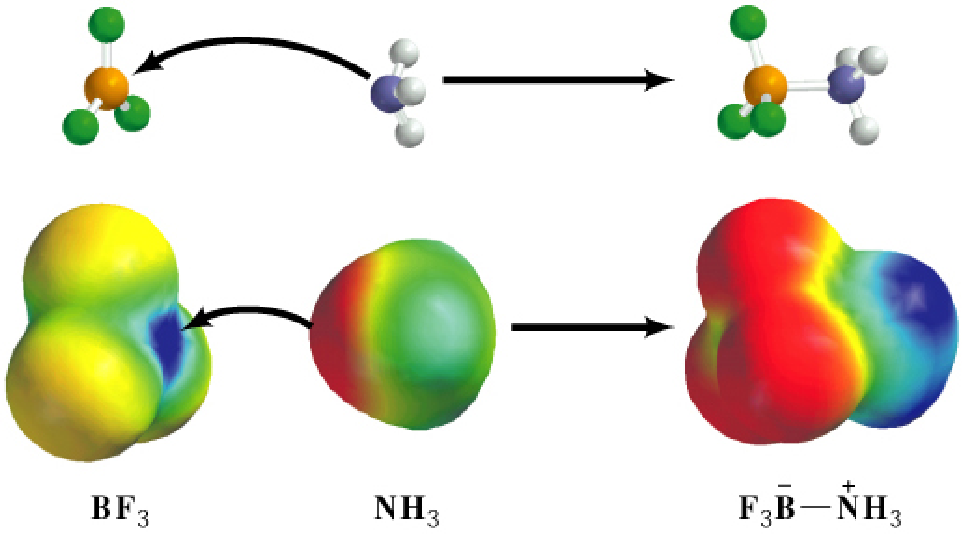
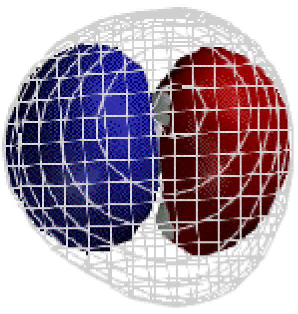
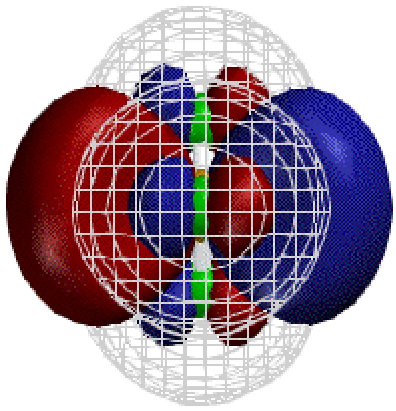


Figure 3.1 **Electrostatic potential maps for BF_3, NH_3, and the product that results from reaction between them. Attraction between the strongly positive region of BF_3 and the negative region of NH_3 causes them to react. The electrostatic potential map for the product for the product shows that the fluorine atoms draw in the electron density of the formal negative charge, and the nitrogen atom, with its hydrogens, carries the formal positive charge.**

2. BF_3 has substantial **positive charge** centered on the **boron** atom and **negative charge** located on the three **fluorine** atoms.
3. NH_3 has substantial **negative charge** localized in the region of its **nonbonding electron** pair.
4. The **nonbonding electron** of ammonia attacks the boron atom of boron trifluoride, filling boron's **valence shell**.
5. **HOMOs** and **LUMOs** in Reactions:
   1) **HOMO:** highest occupied molecular orbital
   2) **LUMO:** lowest unoccupied molecular orbital



HOMO of NH_3

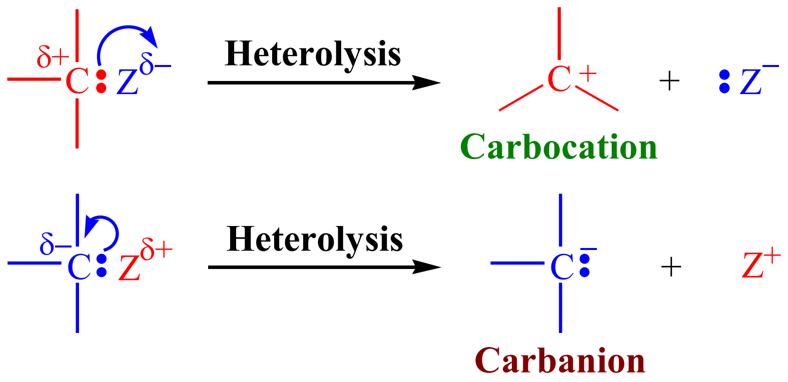


LUMO of BF_3

   3) The nonbonding electron pair occupies the **HOMO** of NH_3.
   4) Most of the volume represented by the **LUMO** corresponds to the empty *p* orbital in the sp^2-hybridized state of BF_3.
   5) The **HOMO** of one molecule interacts with the **LUMO** of another in a reaction.

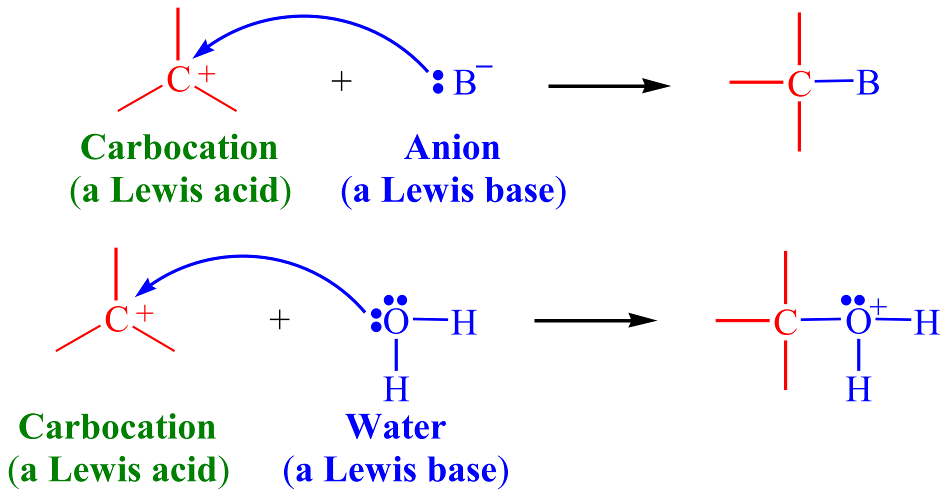
3.3 HETEROLYSIS OF BONDS TO CARBON: CARBOCATIONS AND CARBANIONS

3.3A CARBOCATIONS AND CARBANIONS



1. **Carbocations have six electrons in their valence shell, and are electron deficient. ⇒ Carbocations are Lewis acids.**
   1) Most carbocations are **short-lived** and **highly reactive**.
   2) Carbonium ion (R^+) ⇔ Ammonium ion (R_4N^+)

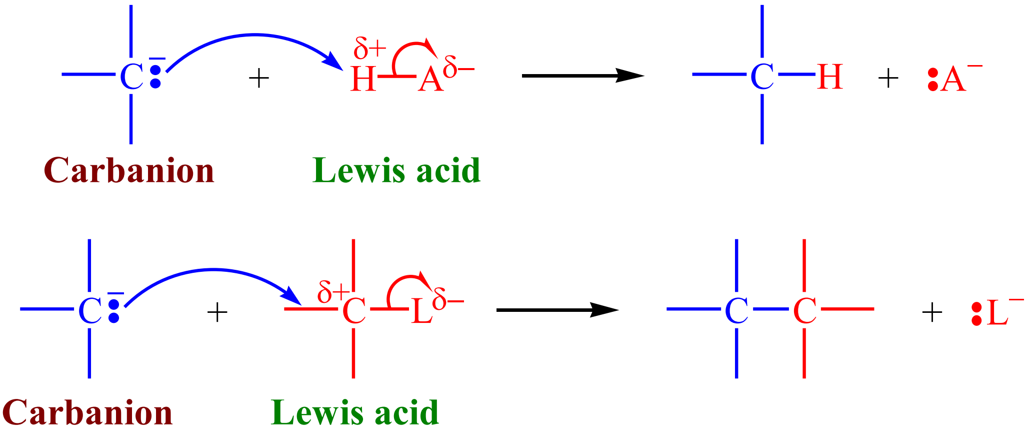
2. Carbocations react rapidly with Lewis bases (molecules or ions that can donate electron pair) to achieve a stable octet of electrons.



3. **Electrophile:** "electron-loving" reagent
   1) Electrophiles seek the extra electrons that will give them a stable valence shell of electrons.
   2) A proton achieves the valence shell configuration of helium; carbocations achieve the valence shell configuration of neon.

4. **Carbanions are Lewis bases.**
   1) Carbanions donate their electron pair to a proton or some other positive center to neutralize their negative charge.

5. **Nucleophile:** “nucleus-loving” reagent



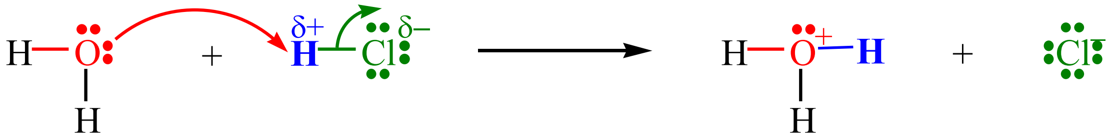
3.4 The Use of Curved Arrows in Illustrating Reactions

3.4A A Mechanism for the Reaction

Reaction:

$$H_2O + HCl \longrightarrow H_3O^+ + Cl^-$$

Mechanism:



A water molecule uses one of the electron pairs to form a bond to a proton of HCl. The bond between the hydrogen and chlorine breaks with the electron pair going to the chlorine atom

This leads to the formation of a hydronium ion and a chloride ion.

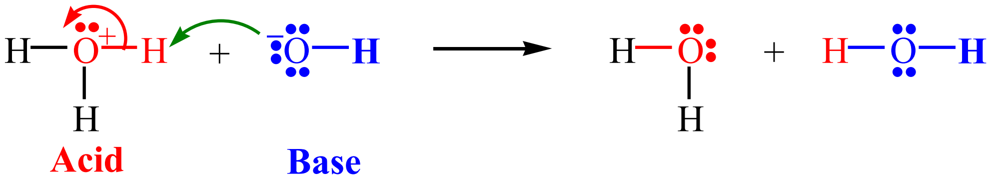
Curved arrows point from electrons to the atom receiving the electrons.

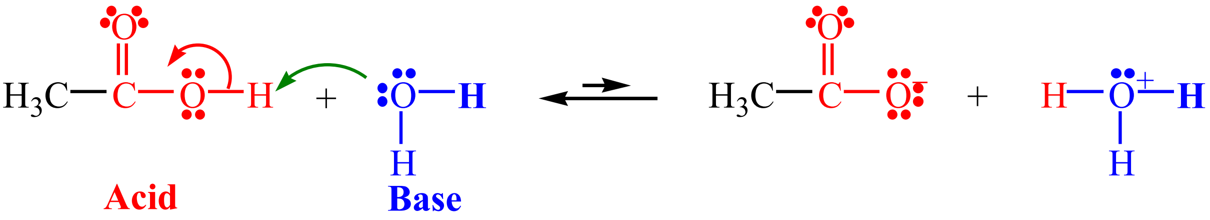
1. **Curved arrow:**

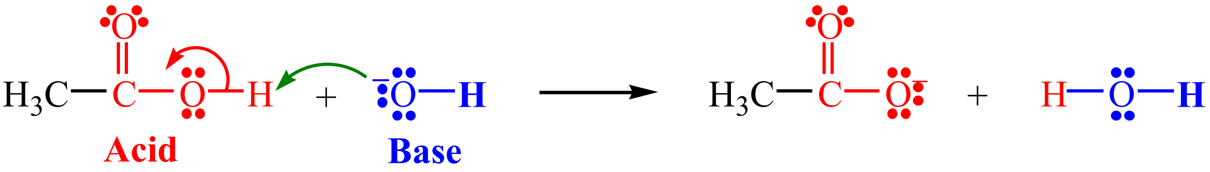
   1) The curved arrow begins with a covalent bond or unshared electron pair (a site of higher electron density) and points toward a site of electron deficiency.

2) The negatively charged electrons of the oxygen atom are attracted to the positively charged proton.

2. Other examples:

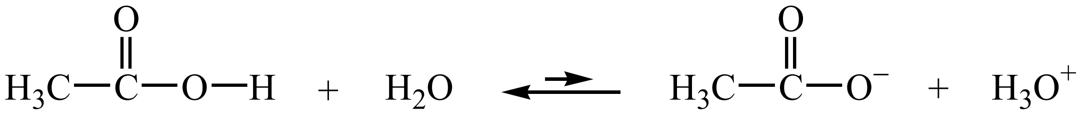






3.5 THE STRENGTH OF ACIDS AND BASES: K_a AND pK_a

1. In a 0.1 *M* solution of acetic acid at 25 °C only 1% of the acetic acid molecules ionize by transferring their protons to water.



3.5A THE ACIDITY CONSTANT, K_a

1. An aqueous solution of acetic acid is an equilibrium:

$$K_{eq} = \frac{[H_3O^+][CH_3CO_2^-]}{[CH_3CO_2H][H_2O]}$$

2. **The acidity constant:**

1) For dilute aqueous solution: water concentration is essentially constant (~ 55.5 *M*)

$$K_a = K_{eq}[H_2O] = \frac{[H_3O^+][CH_3CO_2^-]}{[CH_3CO_2H]}$$

2) At 25 °C, the acidity constant for acetic aicd is 1.76×10^{-5}.

3) General expression for any acid:

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

4) A **large value of K_a** means the acid is a **strong acid**, and a **smaller value of K_a** means the acid is a **weak acid**.

5) If the **K_a** is greater than 10, the acid will be completely dissociated in water.

3.5B ACIDITY AND pK_a

1. **pK_a:** $\mathrm{p}K_a = -\log K_a$

2. pH: $\mathrm{pH} = -\log [H_3O^+]$

3. The **pK_a** for acetic acid is 4.75:

$$\mathrm{p}K_a = -\log (1.76 \times 10^{-5}) = -(-4.75) = 4.75$$

4. The **larger the value of the pK_a, the weaker is the acid**.

CH_3CO_2H	CF_3CO_2H	HCl
pK_a = 4.75	**pK_a = 0.18**	**pK_a = −7**

Acidity increases →

1) For dilute aqueous solution: water concentration is essentially constant (~ 55.5 *M*)

Table 3.1 Relative Strength of Selected Acids and their Conjugate Bases

	Acid	Approximate pK_a	Conjugate Base	
Strongest Acid	$HSbF_6$ (a super acid)	< -12	SbF_6^-	Weakest Base
	HI	−10	I^-	
	H_2SO_4	−9	HSO_4^-	
	HBr	−9	Br^-	
	HCl	−7	Cl^-	
	$C_6H_5SO_3H$	−6.5	$C_6H_5SO_3^-$	
	$(CH_3)_2O^+H$	−3.8	$(CH_3)_2O$	
	$(CH_3)_2C{=}O^+H$	−2.9	$(CH_3)_2C{=}O$	
	$CH_3O^+H_2$	−2.5	CH_3OH	
	H_3O^+	−1.74	H_3O	
	HNO_3	−1.4	HNO_3^-	
	CF_3CO_2H	0.18	$CF_3CO_2^-$	
	HF	3.2	F^-	
	H_2CO_3	3.7	HCO_3^-	
	CH_3CO_2H	4.75	$CH_3CO_2^-$	
	$CH_3COCH_2COCH_3$	9.0	$CH_3COCH^-COCH_3$	
	NH_4^+	9.2	NH_4^+	
	C_6H_5OH	9.9	$C_6H_5O^-$	
	HCO_3^-	10.2	HCO_3^{2-}	
	$CH_3NH_3^+$	10.6	CH_3NH_3	
	H_2O	15.74	HO^-	
	CH_3CH_2OH	16	$CH_3CH_2O^-$	
	$(CH_3)_3COH$	18	$(CH_3)_3CO^-$	
	CH_3COCH_3	19.2	$^-CH_2COCH_3$	
	$HC{\equiv}CH$	25	$HC{\equiv}C^-$	
	H_2	35	H^-	
	NH_3	38	NH_2^-	
	$CH_2{=}CH_2$	44	$CH_2{=}CH^-$	
Weakest Acid	CH_3CH_3	50	$CH_3CH_2^-$	Strongest Base

↑ Increasing acid strength

↓ Increasing base strength

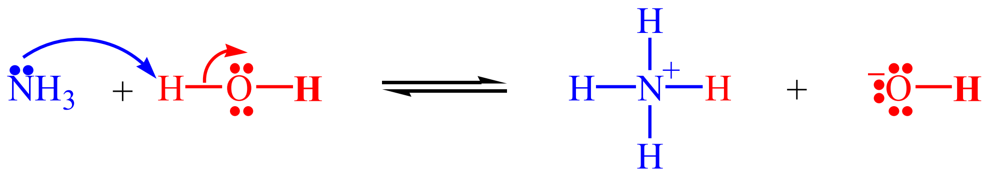
3.5C PREDICTING THE STRENGTH OF BASES

1. **The stronger the acid, the weaker will be its conjugate base.**
2. **The larger the pK_a of the conjugate acid, the stronger is the base.**

Increasing base strength →

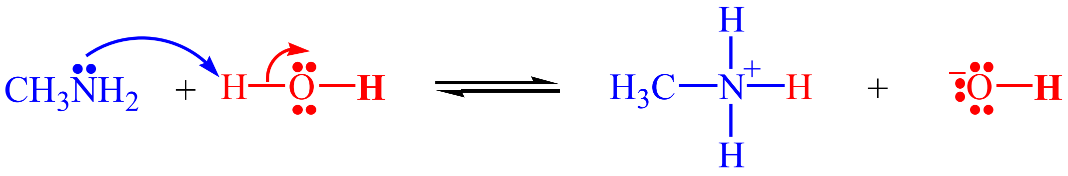
Cl^-	$CH_3CO_2^-$	HO^-
Very weak base		**Strong base**
pK_a of conjugate acid (HCl) = −7	**pK_a of conjugate acid (CH_3CO_2H) = −4.75**	**pK_a of conjugate acid (H_2O) = −15.7**

3. **Amines are weak bases:**



Base **Acid** **Conjugate acid** **Conjugate base**

pK_a = 9.2



Base **Acid** **Conjugate acid** **Conjugate base**

pK_a = 10.6

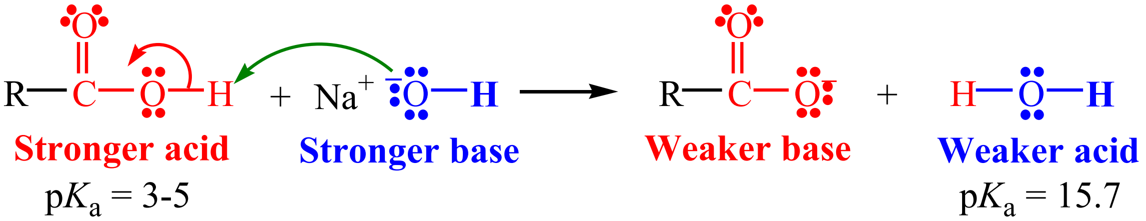
1) The conjugate acids of ammonia and methylamine are the ammonium ion, NH_4^+ (pK_a = 9.2) and the methylammonium ion, $CH_3NH_3^+$ (pK_a = 10.6) respectively. Since methylammonium ion is a weaker acid than ammonium ion, methylamine is a stronger base than ammonia.

3.6 Predicting The Outcome of Acid-Base Reactions

3.6A General order of acidity and basicity:

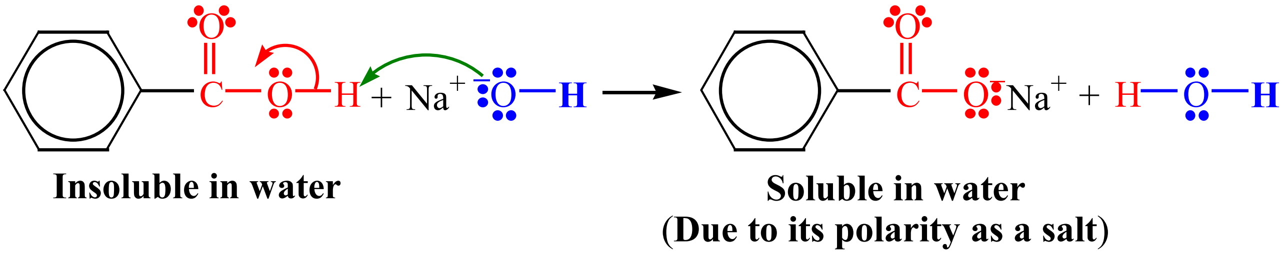
1. **Acid-base reactions always favor the formation of the weaker acid and the weaker base.**

1) **Equilibrium control:** the outcome of an acid-base reaction is determined by the position of an equilibrium.



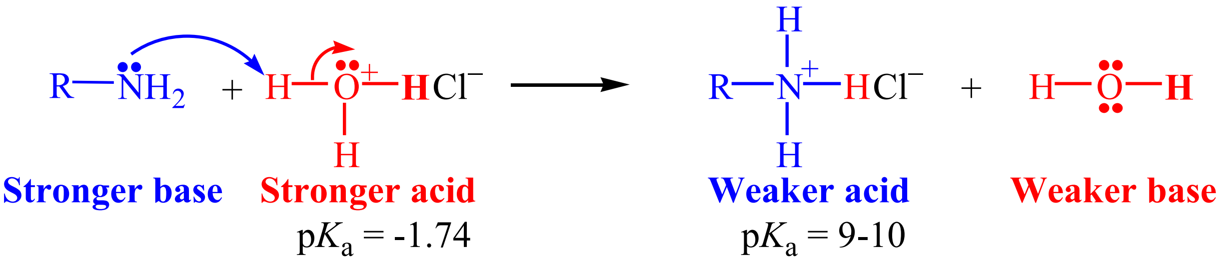
Large difference in pK_a value ⇒ the position of equilibrium will greatly favor the formation of the products (one-way arrow is used)

2. **Water-insoluble carboxylic acids dissolve in aqueous sodium hydroxide:**

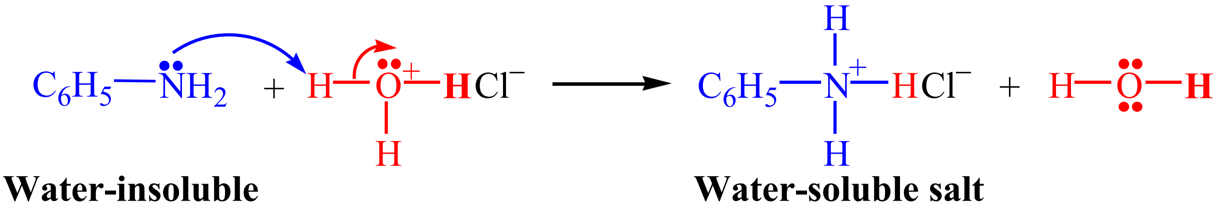


1) Carboxylic acids containing fewer than five carbon atoms are soluble in water.

3. **Amines react with hydrochloric acid:**



4. **Water-insoluble amines dissolve readily in hydrochloric acid:**



1) Amines of lower molecular weight are very soluble in water.

3.7 THE RELATIONSHIP BETWEEN STRUCTURE AND ACIDITY

1. The strength of an acid depends on the extent to which a proton can be separated from it and transferred to a base.

   1) Breaking a bond to the proton ⇒ **the strength of the bond to the proton is the dominating effect**.

   2) Making the conjugate base more electrically negative.

   3) **Acidity increases as we descend a vertical column:**

Acidity increases →

H–F	H–Cl	H–Br	H–I
pK_a = 3.2	pK_a = −7	pK_a = −9	pK_a = −10

← **The strength of H–X bond increases**

   4) **The conjugate bases of strong acids are very weak bases:**

← **Basicity increases**

F^- Cl^- Br^- I^-

2. Same trend for H_2O, H_2S, and H_2Se:

Acidity increases →

H_2O H_2S H_2Se

← **Basicity increases**

HO^- HS^- HSe^-

3. **Acidity increases from left to right when we compare compounds in the same horizontal row of the periodic table.**
   1) **Bond strengths are roughly the same, the dominant factor becomes the electronegativity of the atom bonded to the hydrogen.**
   2) The electronegativity of this atom affects **the polarity of the bond to the proton**, and it affects **the relative stability of the anion** (conjugate base).

4. If **A** is more electronegative than **B** for **H—A** and **H—B**:

$$\overset{\delta+}{H}—\overset{\delta-}{A} \quad \text{and} \quad \overset{\delta+}{H}—\overset{\delta-}{B}$$

   1) Atom **A** is more **negative** than atom **B** ⇒ the proton of **H—A** is more **positive** than that of **H—B** ⇒ the proton of **H—A** will **be held less strongly** ⇒ the proton of **H—A** will **separate and be transferred to a base more readily**.
   2) **A** will **acquire a negative charge more readily** than **B** ⇒ **A**$^-$.anion will be **more stable** than **B**$^-$.anion

5. The acidity of CH_4, NH_3, H_2O, and HF:

Electronegativiity increases →

C　　N　　O　　F

Acidity increases →

$\overset{\delta-}{H_3C}—\overset{\delta+}{H}$	$\overset{\delta-}{H_2N}—\overset{\delta+}{H}$	$\overset{\delta-}{HO}—\overset{\delta+}{H}$	$\overset{\delta-}{F}—\overset{\delta+}{H}$
pK_a = 48	**pK_a = 38**	**pK_a = 15.74**	**pK_a = 3.2**

6. Electrostatic potential maps for CH_4, NH_3, H_2O, and HF:
   1) Almost no positive charge is evident at the hydrogens of methane (pK_a = 48).
   2) Very little positive charge is present at the hydrogens of ammonia (pK_a = 38).
   3) Significant positive charge at the hydrogens of water (pK_a = 15.74).

4) Highest amount of positive charge at the hydrogen of hydrogen fluoride (pK_a = 3.2).

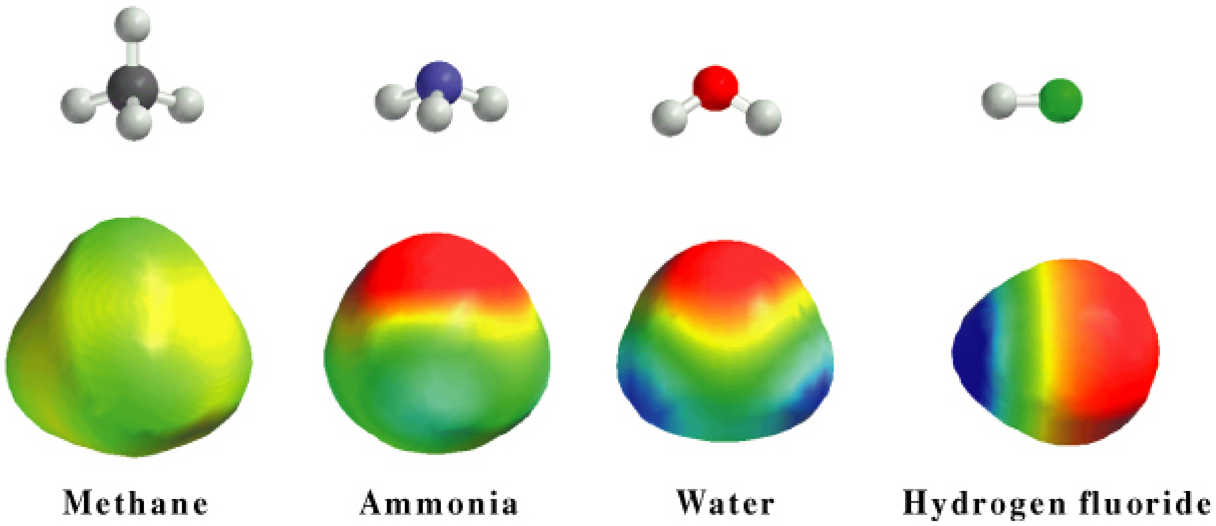
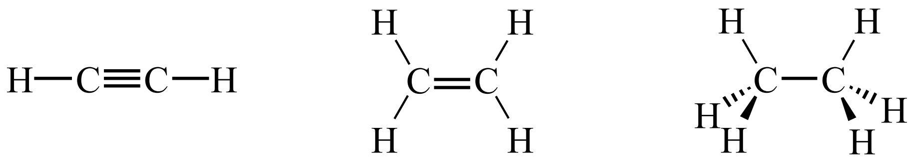


Figure 3.2 The effect of increasing electronegativity among elements from left to right in the first row of the periodic table is evident in these electrostatic potential maps for methane, ammonia, water, and hydrogen fluoride.

CH_3^- H_2N^- HO^- F^-

3.7A THE EFFECT OF HYBRIDIZATION

1. The acidity of ethyne, ethane, and ethane:



Ethyne	**Ethene**	**Ethane**
pK_a = 25	**pK_a = 44**	**pK_a = 50**

1) Electrons of 2*s* orbitals have lower energy than those of 2*p* orbitals because ***electrons in 2s orbitals tend, on the average, to be much closer to the nucleous than electrons in 2p orbitals***.

2) **Hybrid orbitals having more *s* character means that the electrons of the anion will, on the average, be lower in energy, and the anion will be more stable**.

2. **Electrostatic potential maps for ethyne, ethene, and ethane:**

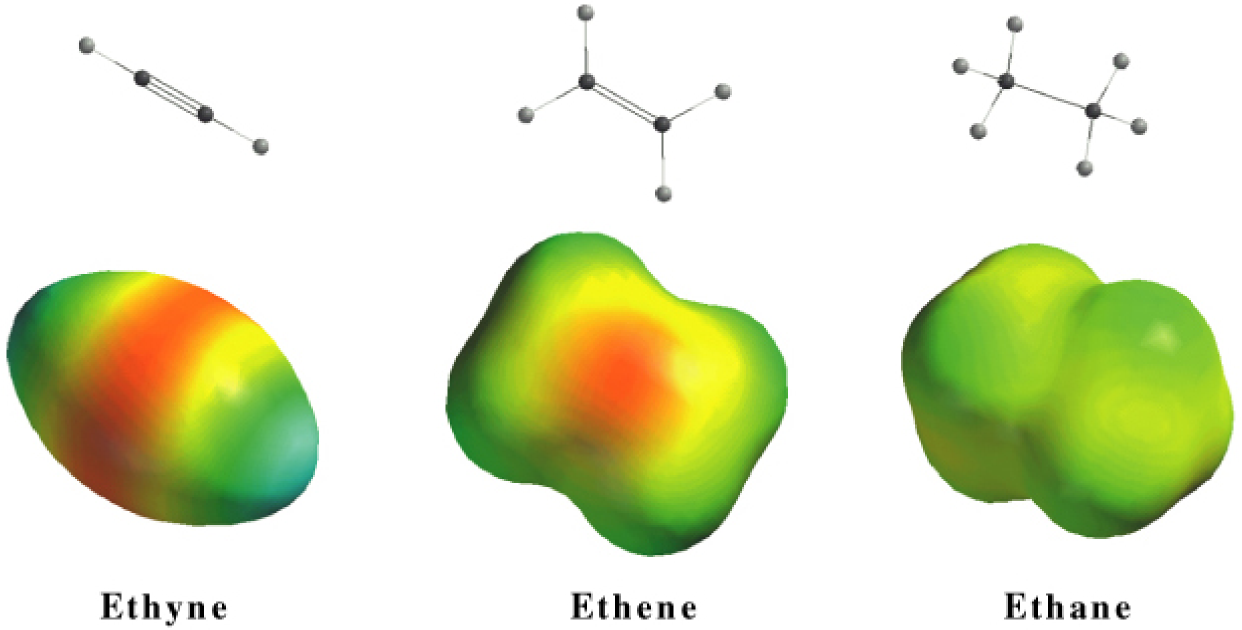


Figure 3.3 Electrostatic potential maps for ethyne, ethene, and ethane.

1) Some positive charge is clearly evident on the hydrogens of ethyne.
2) Almost no positive charge is present on the hydrogens of ethene and ethane.
3) Negative charge resulting from electron density in the π bonds of ethyne and ethene is evident in **Figure 3.3**.
4) The π electron density in the triple bond of ethyne is cylindrically symmetric.

3. ***Relative Acidity of the Hydrocarbon*:**

$$HC{\equiv}CH \quad > \quad H_2C{=}CH_2 \quad > \quad H_3C{-}CH_3$$

4. ***Relative Basicity of the Carbanions*:**

$$H_3C{-}CH_2{:}^- \quad > \quad H_2C{=}CH{:}^- \quad > \quad HC{\equiv}C{:}^-$$

3.7B INDUCTIVE EFFECTS

1. The C—C bond of ethane is completely nonpolar:

$H_3C{-}CH_3$ **Ethane**

The C−C bond is nonpolar.

2. The C—C bond of ethyl fluoride is polarized:

$$\overset{\delta+}{H_3\underset{\mathbf{2}}{C}}{\rightarrow}{-}\overset{\delta+}{\underset{\mathbf{1}}{C}H_2}{\rightarrow}{-}\overset{\delta-}{F}$$

1) **C1** is more positive than **C2** as a result of the electron-attracting ability of the fluorine.

3. **Inductive effect:**

1) **Electron attracting** (or **electron withdrawing**) **inductive effect**

2) **Electron donating** (or **electron releasing**) **inductive effect**

4. **Electrostatic potential map:**

1) **The distribution of negative charge around the electronegative fluorine is evident.**

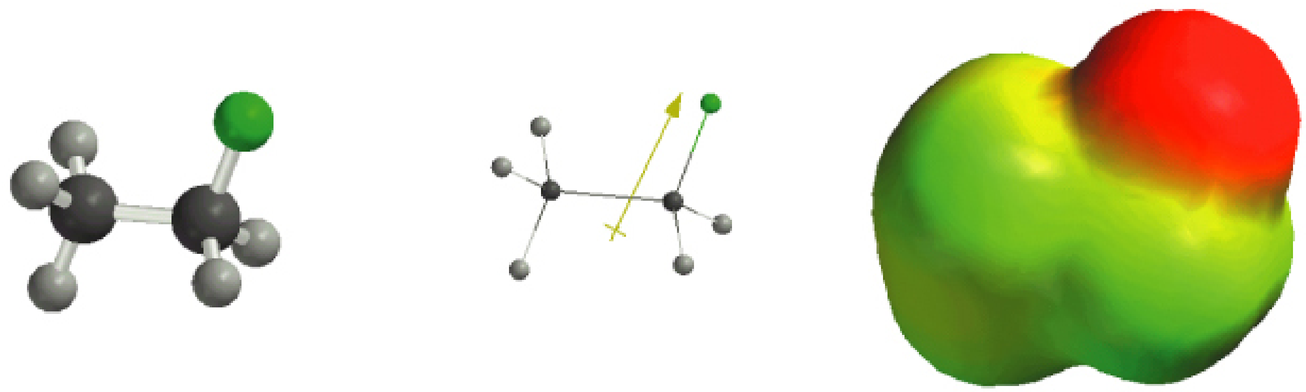


Figure 3.4 Ethyl fluoride (fluoroethane): structure, dipole moment, and charge distribution.

3.8 ENERGY CHANGES

1. **Kinetic energy** and **potential energy**:

1) **Kinetic energy** is the energy an object has because of its motion.

$$K.E. = \frac{mv^2}{2}$$

2) **Potential energy** is stored energy.

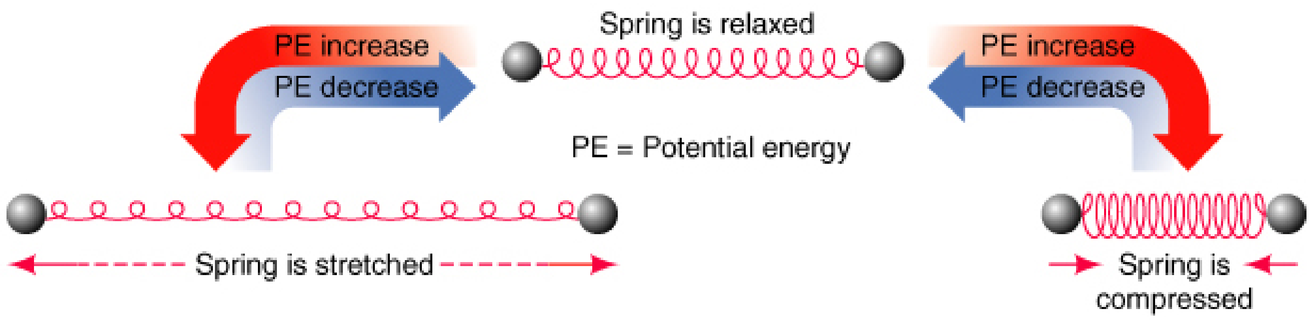


Figure 3.5 Potential energy (PE) exists between objects that either attract or repel each other. When the spring is either stretched or compressed, the PE of the two balls increases.

2. **Chemical energy** is a form of potential energy.

1) It exists because attractive and repulsive electrical forces exist between different pieces of the molecule.

2) Nuclei attract electrons, nuclei repel each other, and electrons repel each other.

3. **Relative potential energy**:

1) The **relative stability** of a system is inversely related to its relative potential energy.

2) The **more potential energy** an object has, the **less stable** it is.

3.8A POTENTIAL ENERGY AND COVALENT BONDS

1. **Formation of covalent bonds:**

$$H\bullet \quad + \quad H\bullet \longrightarrow H{-}H \qquad \Delta H° = -435 \text{ kJ mol}^{-1}$$

1) The **potential energy** of the atoms decreases by 435 kJ mol^{-1} as the covalent bond forms.

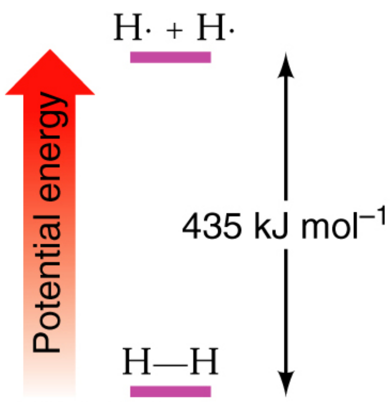


Figure 3.6 The relative potential energies of hydrogen atoms and a hydrogen molecule.

2. **Enthalpies** (**heat contents**), *H*: (***Enthalpy*** comes from *en* + Gk: *thalpein* to heat)
3. **Enthalpy change, ΔH°:** the difference in relative enthalpies of reactants and products in a chemical change.

1) **Exothermic** reactions have ***negative*** ΔH°.

2) **Endothermic** reactions have ***positive*** ΔH°.

3.9 THE RELATIONSHIP BETWEEN THE EQUILIBRIUM CONSTANT AND THE STANDARD FREE-ENERGY CHANGE, Δ*G*°

3.9A Gibbs Free-energy

1. **Standard free-energy change** (**Δ*G*°**):

$$\Delta G° = -2.303\, RT \log K_{eq}$$

1) The unit of energy in SI units is the joule, J, and 1 cal = 4.184 J.

2) A kcal is the amount of energy in the form of heat required to raise the

temperature of 1 Kg of water at 15 °C by 1 °C.

3) The reactants and products are in their standard states: 1 atm pressure for a gas, and 1 *M* for a solution.

2. **Negative value of Δ*G*°: favor the formation of products** when equilibrium is reached.

1) The K_{eq} is larger than 1.

2) Reactions with a Δ*G*° more negative than about 13 kJ mol^{-1} (3.11 kcal mol^{-1}) are said to ***go to completion***, meaning that almost all (>99%) of the reactants are converted into products when equilibrium is reached.

3. **Positive value of Δ*G*°: unfavor the formation of products** when equilibrium is reached.

1) The K_{eq} is less than 1.

4. $\Delta G° = \Delta H° - T\Delta S°$

1) Δ*S*°: changes in the relative order of a system.

i) A positive entropy change (+Δ*S*°): a change from a more ordered system to a less ordered one.

ii) A negative entropy change (−Δ*S*°): a change from a less ordered system to a more ordered one.

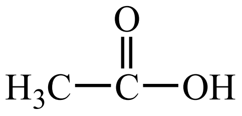
iii) A **positive entropy change** (from order to disorder) makes a **negative contribution to Δ*G*°** and is energetically **favorable** for the **formation of products**.

2) For many reactions in which the number of molecules of products equals the number of molecules of reactants ⇒ **the entropy change is small** ⇒ **Δ*G*° will be determined by Δ*H*°** except at high temperatures.

3.10 THE ACIDITY OF CARBOXYLIC ACIDS

1. **Carboxylic acids are much more acidic than the corresponding alcohols:**

1) pK_as for R–COOH are in the range of 3-5;.pK_as for R–OH are in the range of 15-18.



Acetic acid
pK_a = 4.75
$\Delta G°$ = 27 kJ mol^{-1}

Ethanol
pK_a = 16
$\Delta G°$ = 90.8 kJ mol^{-1}

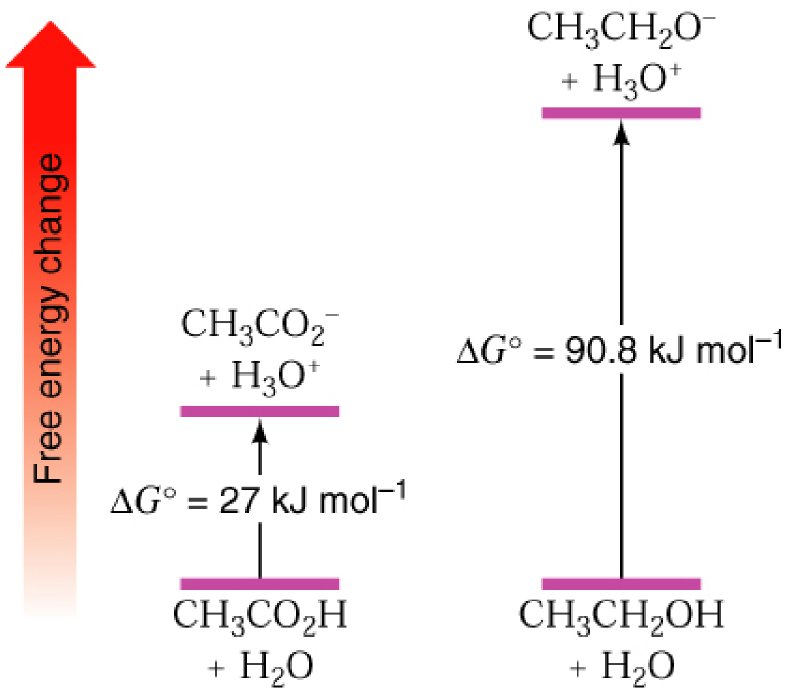
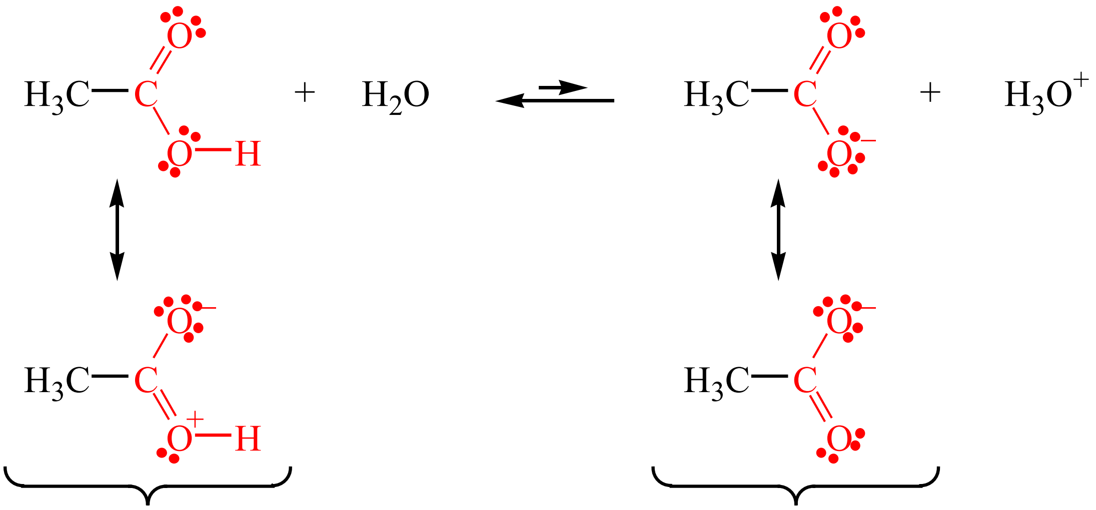


Figure 3.7 **A diagram comparing the free-energy changes that accompany ionization of acetic acid and ethanol. Ethanol has a larger positive free-energy change and is a weaker acid because its ionization is more unfavorable.**

3.10A An Explanation Based on Resonance Effects

1. **Resonance stabilized acetate anion:**

Acetic Acid **Aceate Ion**



Small resonance stabilization

(*The structures are not equivalent and the lower structure requires charge separation.*)

Largeresonance stabilization

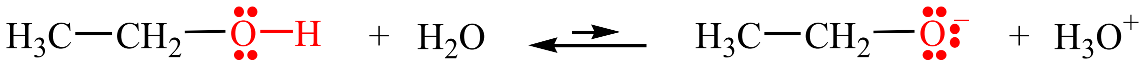
(*The structures are equivalent and there is no requirement for charge separation.*)

Figure 3.8 Two resonance structures that can be written for acetic acid and two that can be written for acetate ion. According to a resonance explanation of the greater acidity of acetic acid, the equivalent resonance structures for the acetate ion provide it greater resonance stabilization and reduce the positive free-energy change for the ionization.

1) The greater stabilization of the carboxylate anion (relative to the acid) lowers the free energy of the anion and thereby decreases the positive free-energy change required for the ionization.

2) **Any factor that makes the free-energy change for the ionization of an acid less positive (or more negative) makes the acid stronger.**

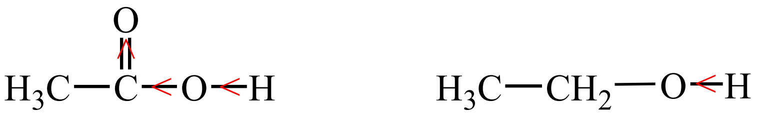
2. **No resonance stabilization for an alcohol and its alkoxide anion:**



No resonance stabilization **No resonance stabilization**

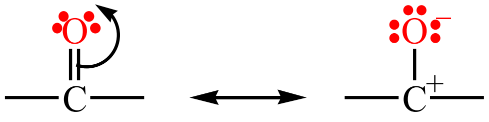
3.10B AN EXPLANATION BASED ON INDUCTIVE EFFECTS

1. **The inductive effect of the carbonyl group** (C=O group) is responsible for the acidity of carboxylic acids.



Acetic acid (Stronger acid) **Ethanol (Weaker acid)**

   1) In both compounds the O—H bond is highly polarized by the greater electronegativity of the oxygen atom.
   2) The carbonyl group has a more powerful electron-attracting inductive effect than the CH_2 group.
   3) The carbonyl group has two resonance structures:



Resonance structures for the carbonyl group

   4) *The second resonance structure above is an important contributor to the overall resonance hybrid.*
   5) The carbon atom of the carbonyl group of acetic acid bears **a large positive charge**, it adds its electron-withdrawing inductive effect to that of the oxygen atom of the hydroxyl group attached to it.
   6) **These combined effects make the hydroxyl proton much more positive than the proton of the alcohol.**

2. The electron-withdrawing inductive effect of the carbonyl group also stabilizes the acetate ion, and therefore **the acetate ion is a weaker base than the ethoxide ion**.

Acetate anion **(Weaker base)** **Ethoxide anion** **(Stronger base)**

3. The electrostatic potential maps for the acetate and the ethoxide ions:

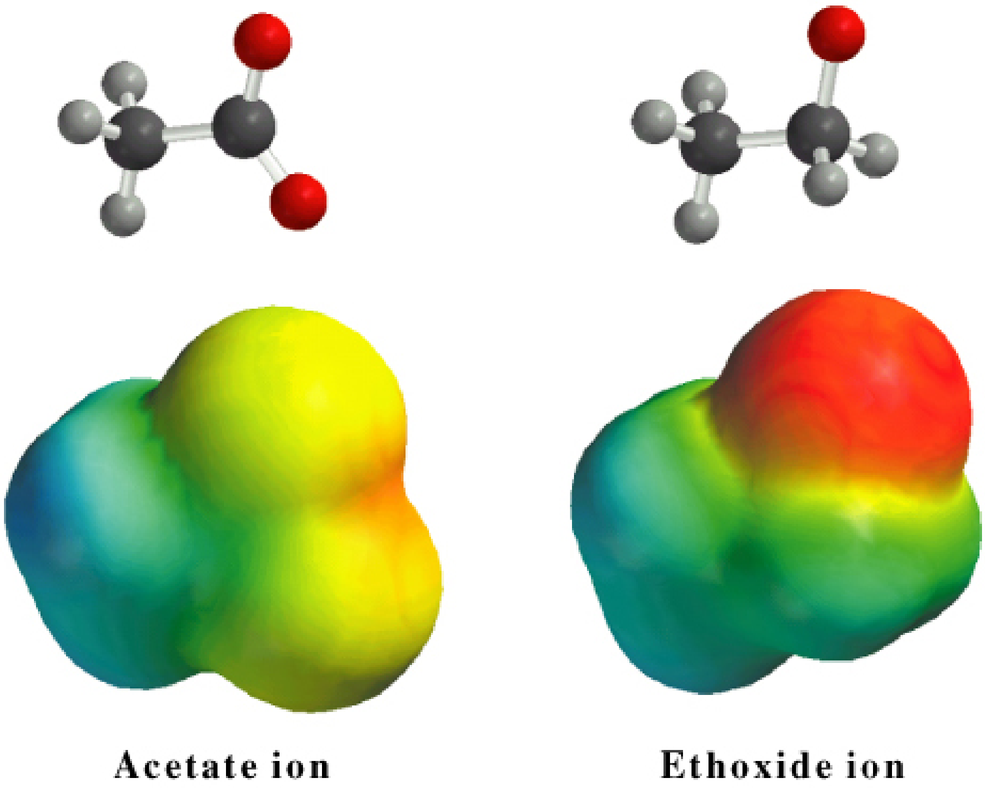


Figure 3.9 Calculated electrostatic potential maps for acetate anion and ethoxide anion. Although both molecules carry the same –1 net charge, acetate stabilizes the charge better by dispersing it over both oxygens.

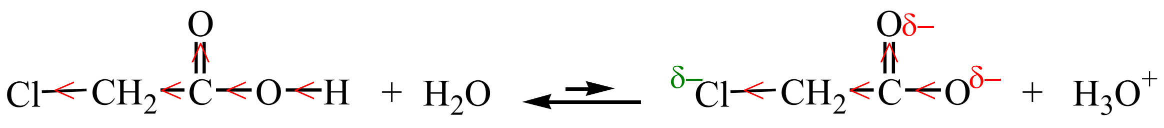
1) The negative charge in acetate anion is evenly distributed over the two oxygens.
2) The negative charge is localized on its oxygen in ethoxide anion.
3) The ability to better stabilize the negative charge makes the acetate a weaker base than ethoxide (and hence its conjugate acid stronger than ethanol)..

3.10C INDUCTIVE EFFECTS OF OTHER GROUPS

1. Acetic acid and chloroacetic acid:

pK_a = 4.75 **pK_a = 2.86**

1) The extra electron-withdrawing inductive effect of the electronegative **chlorine atom** is responsible for the greater acidity of chloroacetic acid by making the hydroxyl proton of chloroacetic acid even **more positive** than that of acetic acid.
2) It stabilizes the chloroacetate ion by **dispersing its negative charge**.



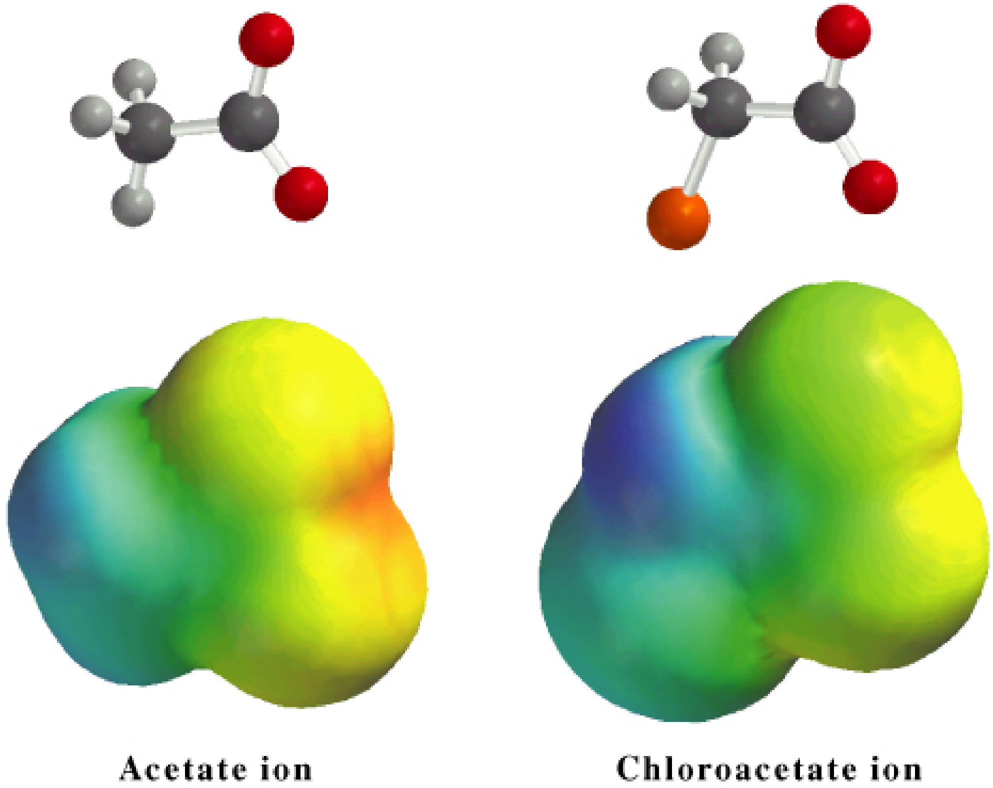
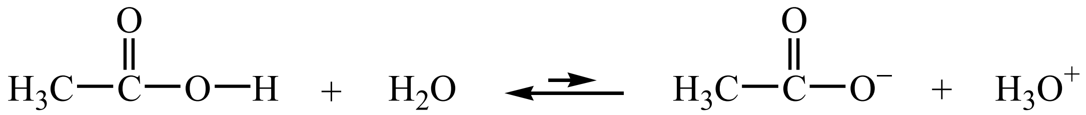


Figure 3.10 The electrostatic potential maps for acetate and chloroacetate ions show the relatively greater ability of chloroacetate to disperse the negative charge.

3) **Dispersal of charge always makes a species more stable.**
4) **Any factor that stabilizes the conjugate base of an acid increases the strength of the acid.**

3.11 THE EFFECT OF THE SOLVENT ON ACIDITY

1. In the absence of a solvent (i.e., in the gas phase), most acids are far weaker than they are in solution. For example, acetic acid is estimated to have a pK_a of about 130 in the gas phase.



1) **In the absence of a solvent, separation of the ions is difficult.**
2) **In solution, solvent molecules surround the ions, insulating them from one another, stabilizing them, and making it far easier to separate them than in the gas phase.**

3.11A Protic and Aprotic solvents

1. **Protic solvent:** a solvent that has a **hydrogen atom attached to a strongly electronegative element** such as oxygen or nitrogen.
2. **Aprotic solvent:**
3. Solvation by hydrogen bonding is important in protic solvent:
   1) Molecules of a protic solvent can form **hydrogen bonds** to the unshared electron pairs of oxygen atoms of an acid and its conjugate base, but **they may not stabilize both equally**.
   2) Hydrogen bonding to $CH_3CO_2^-$ is much stronger than to CH_3CO_2H because the water molecules are more attracted by the negative charge.

4. Solvation of any species decreases the entropy of the solvent because the solvent molecules become much more ordered as they surround molecules of the solute.

   1) Solvation of $CH_3CO_2^-$ is stronger ⇒ the the solvent molecules become more orderly around it ⇒ the entropy change ($\Delta S°$) for the ionization of acetic acid is negative ⇒ the $-T\Delta S°$ makes a positive contribution to $\Delta G°$ ⇒ weaker acid.

2) **Table 3.2** shows, the $-T\Delta S°$ term contributes more to $\Delta G°$ than $\Delta H°$ does ⇒ the free-energy change for the ionization of acetic acid is positive (unfavorable).

3) Both $\Delta H°$ and $-T\Delta S°$ are more favorable for the ionization of chloroacetic acid. The larger contribution is in the entropy term.

4) Stabilization of the chloroacetate anion by the chlorine atom makes the chloroacetate ion less prone to cause an ordering of the solvent because it requires less stabilization through solvation.

Table 3.2 Thermodynamic Values for the Dissociation of Acetic and Chloroacetic Acids in H_2O at 25 °C

Acid	pK_a	$\Delta G°$ (kJ mol^{-1})	$\Delta H°$ (kJ mol^{-1})	$-T\Delta S°$ (kJ mol^{-1})
CH_3CO_2H	4.75	+27	–0.4	+28
$ClCH_2CO_2H$	2.86	+16	–4.6	+21

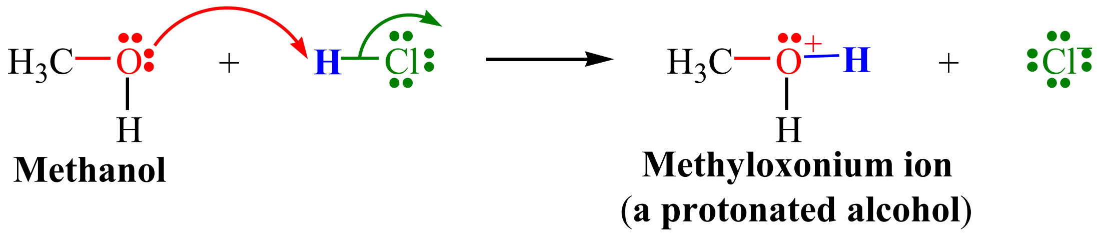
Table Explanation of thermodynamic quantities: $\Delta G° = \Delta H° - T\Delta S°$

Term	Name	Explanation
$\Delta G°$	Gibbs free-energy change (*kcal*/*mol*)	Overall energy difference between reactants and products. When $\Delta G°$ is negative, a reaction can occur spontaneously. $\Delta G°$ is related to the equilibrium constant by the equation: $\Delta G° = -RT\ln K_{eq}$
$\Delta H°$	Enthalpy change (*kcal*/*mol*)	Heat of reaction; the energy difference between strengths of bonds broken in a reaction and bonds formed
$\Delta S°$	Entropy change (*cal*/*degree*×*mol*)	Overall change in freedom of motion or “disorder” resulting from reaction; usually much smaller than $\Delta H°$

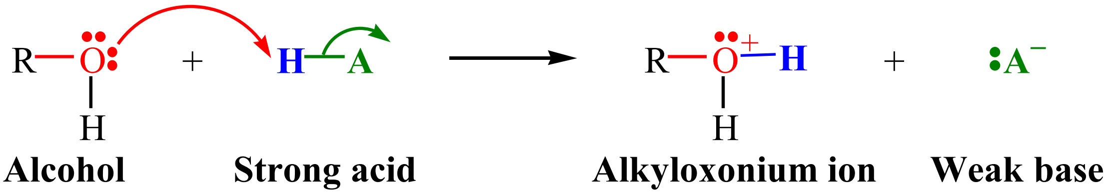
3.12 ORGANIC COMPOUNDS AS BASES

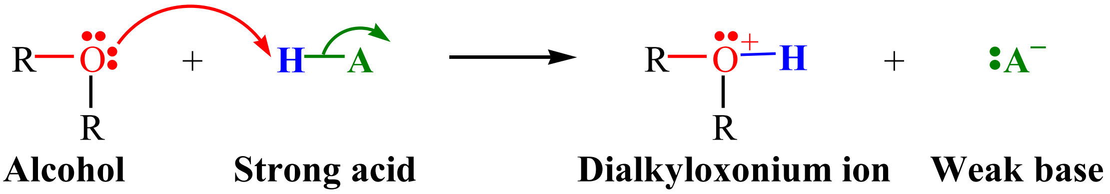
3.12A Organic Bases

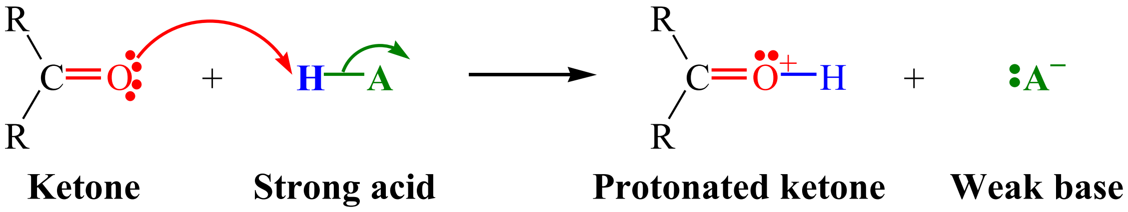
1. An organic compound contains an atom with an unshared electron pair is a potential base.

1) 

i) The conjugate acid of the alcohol is called a **protonated alcohol** (more formally, **alkyloxonium ion**).

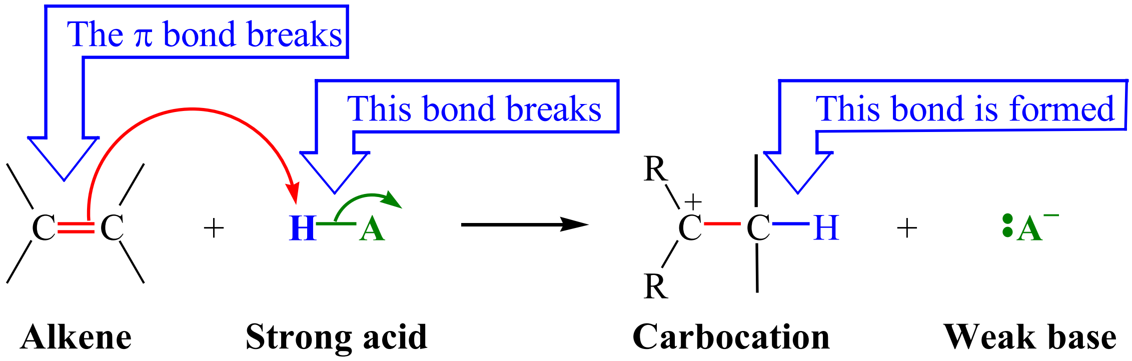
2) 

3) 

4) 

5) **Proton transfer reactions are often the first step in many reactions that alcohols, ethers, aldehydes, ketones, esters, amides, and carboxylic acids undergo.**

6) The π bond of an alkene can act as a base:

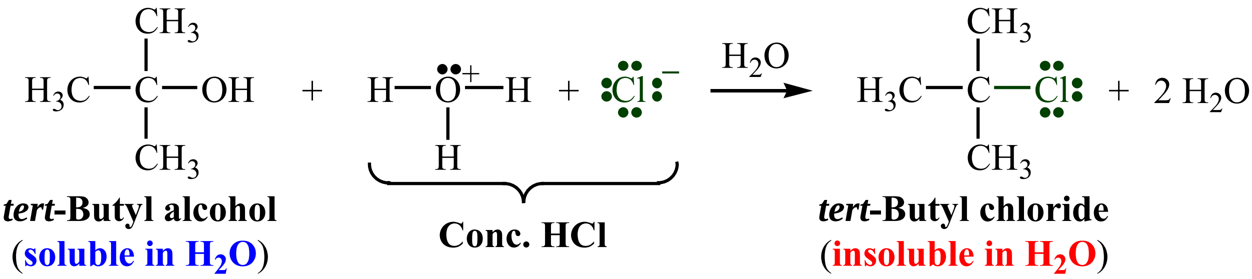


i) The π bond of the double bond and the bond between the proton of the acid and its conjugate base are broken; a bond between a carbon of the alkene and the proton is formed.

ii) A **carbocation** is formed.

3.13 A MECHANISM FOR AN ORGANIC REACTION

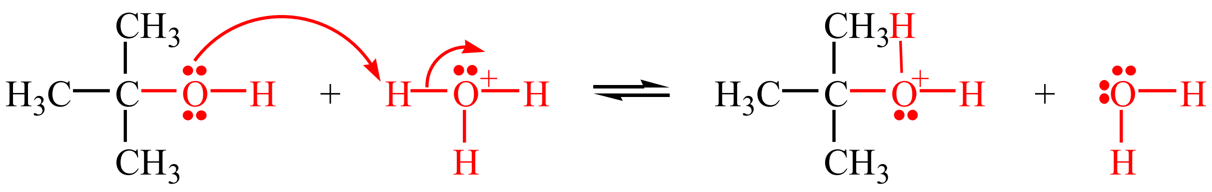
1.



A Mechanism for the Reaction

Reaction of *tert*-Butyl Alcohol with Concentrated Aqueous HCl:

Step 1

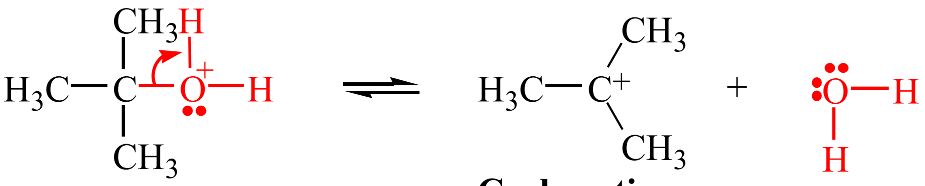


***tert*-Butyloxonium ion**

***tert*-Butyl alcohol acts as a base and accepts a proton from the hydronium ion.**

The product is a protonated alcohol and water (the conjugate acid and base).

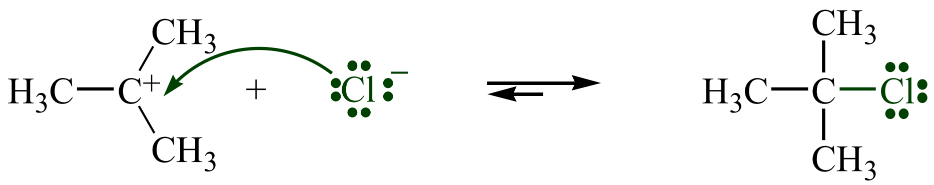
Step 2



Carbocation

The bond between the carbon and oxygen of the *tert*-butyloxonium ion breaks heterolytically, leading to the formation of a carbocation and a molecule of water.

Step 3



***tert*-Butyl chloride**

The carbocation, acting as a Lewis acid, accepts an electron pair from a chloride ion to become the product.

2. Step 1 is a straightforward Brønsted acid-base reaction.

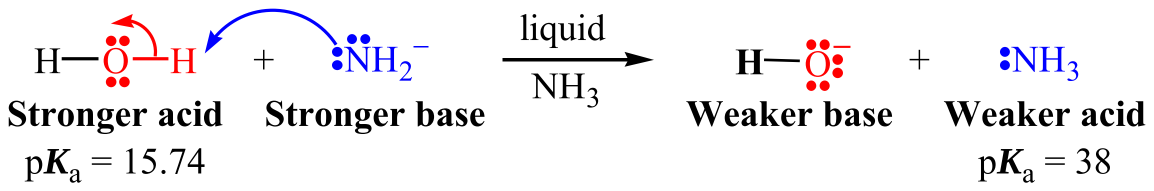
3. Step 2 is the reverse of a Lewis acid-base reaction. (The presence of a formal positive charge on the oxygen of the protonated alcohol weakens the

carbon-oxygen by drawing the electrons in the direction of the positive oxygen.)

4. Step 3 is a Lewis acid-base reaction.

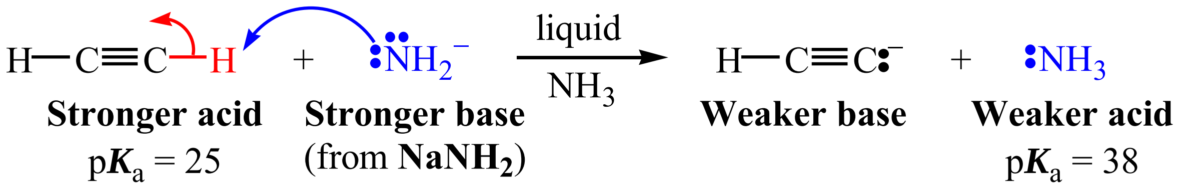
3.14 ACIDS AND BASES IN NONAQUEOUS SOLUTIONS

1. The amide ion (NH_2^-) of sodium amide ($NaNH_2$) is a very powerful base:

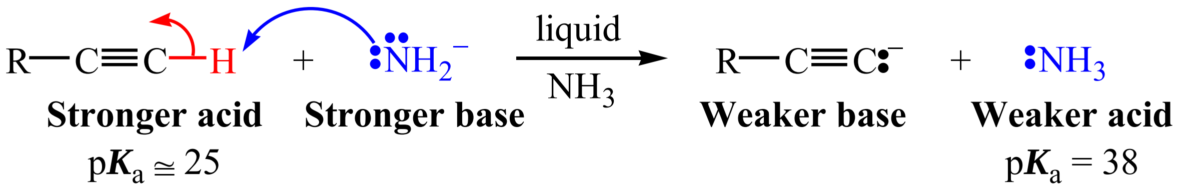


1) **Leveling effect**: the **strongest base** that can exist in aqueous solution in significant amounts is the **hydroxide** ion.

2. In solvents other than water such as hexane, diethyl ether, or liquid ammonia (b.p. –33 °C), bases stronger than hydroxide ion can be used. All of these solvents are **very weak acids**.



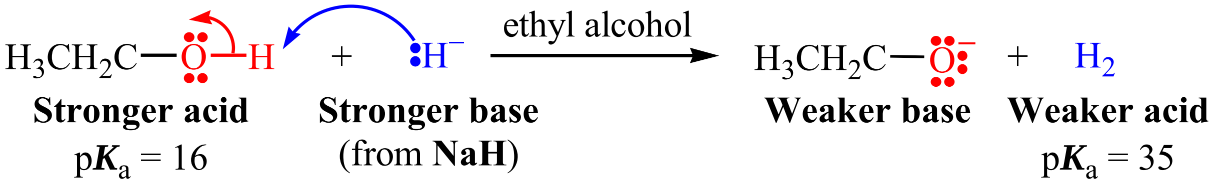
1) **Terminal alkynes**:



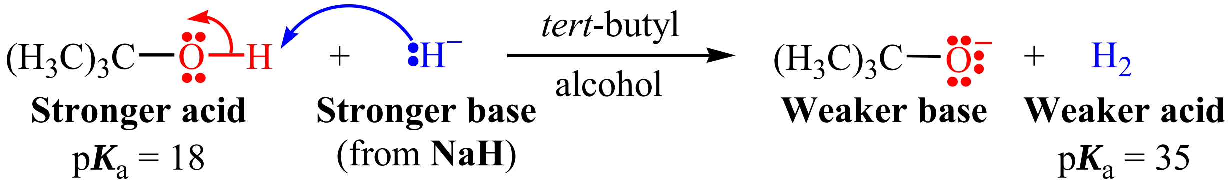
3. **Alkoxide ions (RO^-)** are the conjugate bases when alcohols are utilized as solvents.

1) Alkoxide ions are somewhat **stronger bases** than hydroxide ions because alcohols are weaker acids than water.

2) Addition of sodium hydride (NaH) to ethanol produces a solution of sodium ethoxide (CH_3CH_2ONa) in ethanol.

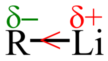


3) Potassium *tert*-butoxide ions, $(CH_3)_3COK$, can be generated similarily.

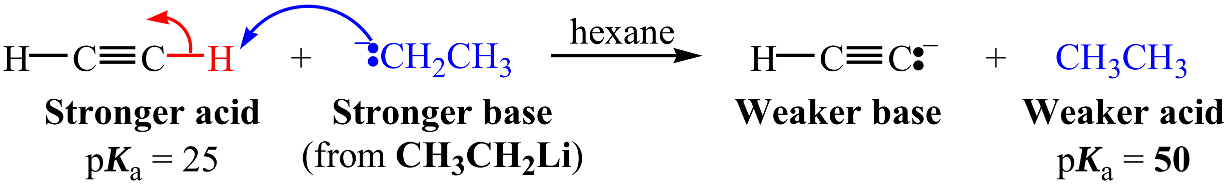


4. **Alkyllithium** (**RLi**):

1) The C—Li bond has covalent character but is highly polarized to make the carbon negative.



2) Alkyllithium react as though they contain alkanide (**R:**⁻) ions (or alkyl carbanions), the conjugate base of alkanes.



3) Alkyllithium can be easily prepared by reacting an alkyl halide with lithium metal in an ether solvent.

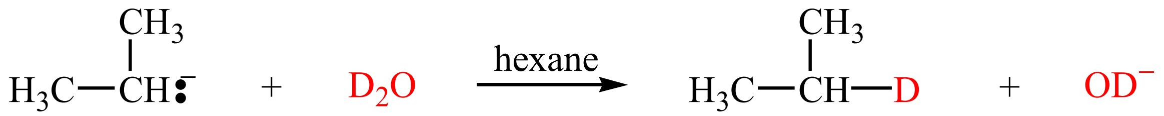
3.15 ACIDS-BASE REACTIONS AND THE SYNTHESIS OF

DEUTERIUM- AND TRITIUM-LABELED COMPOUNDS

1. Deuterium (^{2}**H**) and tritium (^{3}**H**) label:
   1) For most chemical purposes, deuterium and tritium atoms in a molecule behave in much the same way that ordinary hydrogen atoms behave.
   2) The extra mass and additional neutrons of a deuterium or tritium atom make its position in a molecule easy to locate.
   3) Tritium is radioactive which makes it very easy to locate.

2. **Isotope effect**:
   1) The extra mass associated with these labeled atoms may cause compounds containing deuterium or tritium atoms to react more slowly than compounds with ordinary hydrogen atoms.
   2) Isotope effect has been useful in studying the mechanisms of many reactions.

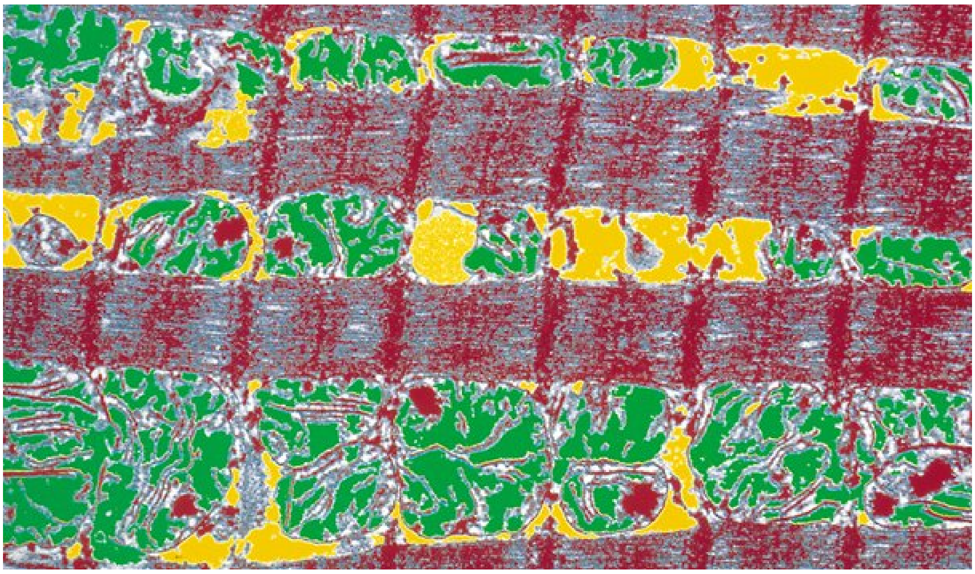
3. Introduction of deuterium or tritium atom into a specific location in a molecule:



Isopropyl lithium (*stronger base*) (*stronger acid*) **2-Deuteriopropane** (*weaker acid*) (*weaker base*)

Alkanes: Nomenclature, Conformational Analysis, and an Introduction to Synthesis

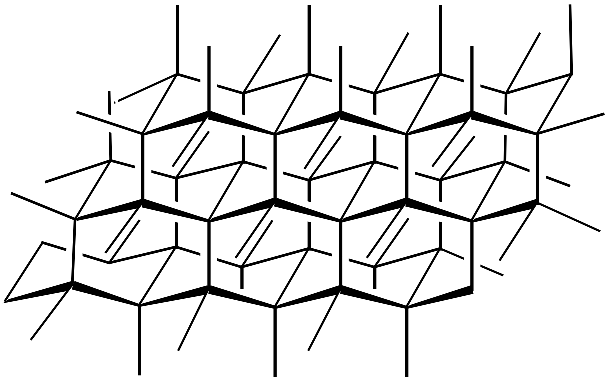
To Be flexible or Inflexible —— Molecular structure Makes the difference



Electron micrograph of myosin

1. When your muscles contract it is largely because many **C–C sigma** (single) bonds are undergoing **rotation** (**conformational changes**) in a muscle protein called **myosin** (肌蛋白質、肌球素).

2. When you etch glass with a **diamond**, the **C–C single bonds** are **resisting all the forces** brought to bear on them such that the glass is scratched and not the diamond.



3. **Nanotubes**, a new class of carbon-based materials with **strength** roughly **one hundred times** that of **steel**, also have an exceptional toughness.
4. The properties of these materials depends on many things, but **central to them is whether or not rotation is possible around C–C bonds**.

4.1 INTRODUCTION TO ALKANES AND CYCLOALKANES

1. **Hydrocarbons:**
   1) **Alkanes:** C_nH_{2n+2} (saturated)
      i) **Cycloalkanes:** C_nH_{2n} (containing a single ring)
      ii) Alkanes and cycloalkanes are so similar that many of their properties can be considered side by side.
   2) **Alkenes:** C_nH_{2n} (containing one double bond)
   3) **Alkynes:** C_nH_{2n-2} (containing one triple bond)

4.1A SOURCES OF ALKANES: PETROLEUM

1. The primary source of alkanes is petroleum.

4.1B PETROLEUM REFINING

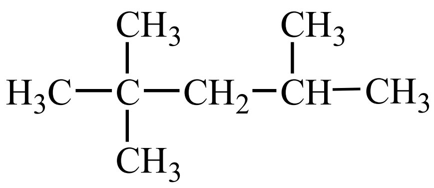
1. The first step in refining petroleum is distillation.
2. More than 500 different compounds are contained in the petroleum distillates boiling below 200 °C, and many have almost the same boiling points.
3. Mixtures of alkanes are suitable for uses as fuels, solvents, and lubricants.
4. Petroleum also contains small amounts of oxygen-, nitrogen-, and sulfur-containing compounds.

Table 4.1 Typical Fractions Obtained by distillation of Petroleum

Boiling Range of Fraction (°C)	Number of Carbon Atoms per Molecules	Use
Below 20	C_1–C_4	Natural gas, bottled gas, petrochemicals
20–60	C_5–C_6	Petroleum ether, solvents
60–100	C_6–C_7	Ligroin, solvents
40–200	C_5–C_{10}	Gasoline (straight-run gasoline)
175–325	C_{12}–C_{18}	Kerosene and jet fuel
250–400	C_{12} and higher	Gas oil, fuel oil, and diesel oil
Nonvolatile liquids	C_{20} and higher	Refined mineral oil, lubricating oil, grease
Nonvolatile solids	C_{20} and higher	Paraffin wax, asphalt, and tar

4.1C CRACKING

1. **Catalytic cracking:** When a mixture of alkanes from the gas oil fraction (C_{12} and higher) is heated at very high temperature (~500 °C) in the presence of a variety of catalysts, the molecules break apart and rearrange to smaller, more highly branched alkanes containing 5-10 carbon atoms.
2. **Thermal cracking:** tend to produce unbranched chains which have very low "octane rating".
3. **Octane rating:**
   1) **Isooctane:** 2,2,4-trimethylpentane burns very smoothly in internal combustion engines and has an octane rating of 100.

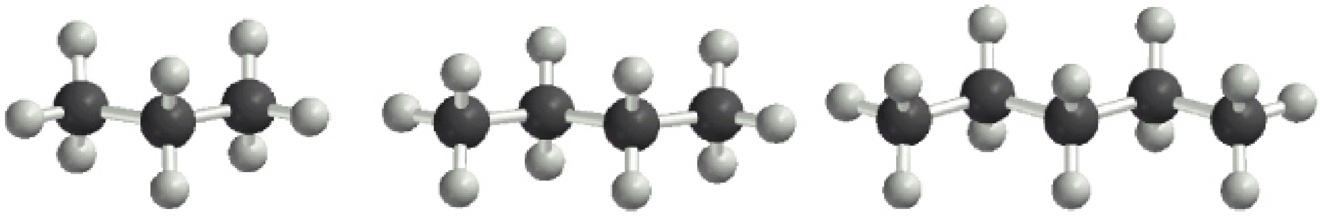


2,2,4-trimethylpentane (**"isooctane"**)

   2) **Heptane** [$CH_3(CH_2)_5CH_3$]**:** produces much knocking when it is burned in internal combustion engines and has an octane rating of 0.

4.2 SHAPES OF ALKANES

1. Tetrahedral orientation of groups is the rule for the carbon atoms of all alkanes and cycloalkanes (sp^3 hybridization).



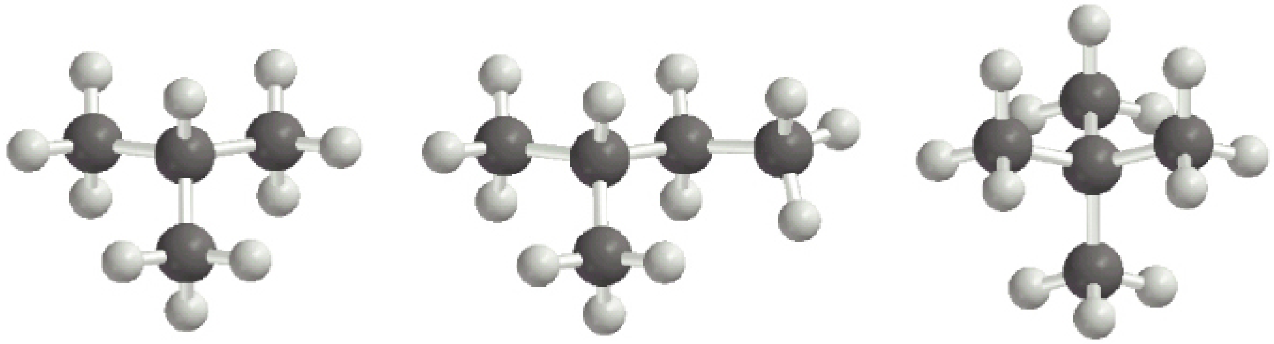
Propane $CH_3CH_2CH_3$ **Butane** $CH_3CH_2CH_2CH_3$ **Pentane** $CH_3CH_2CH_2CH_2CH_3$

Figure 4.1 Ball-and-stick models for three simple alkanes.

2. The carbon chains are ***zigzagged*** ⇒ **unbranched** alkanes ⇒ contain only 1° and 2° carbon atoms.

3. **Branched-chain** alkanes:

4. Butane and isobutene are **constitutional-isomers**.

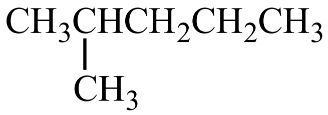
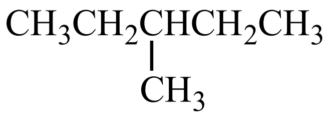
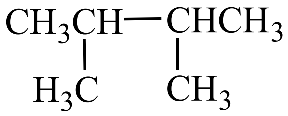
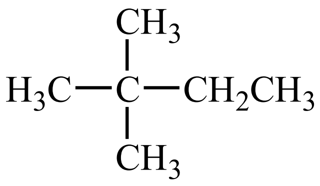


$H_3C-CH(CH_3)-CH_3$ **Isobutane** $H_3C-CH(CH_3)-CH_2-CH_3$ **Isopentane** $H_3C-C(CH_3)_2-CH_3$ **Neopentane**

Figure 4.2 Ball-and-stick models for three branched-chain alkanes. In each of the compounds one carbon atom is attached to more than two other carbon atoms.

5. Constitutional-isomers have different physical properties.

Table 4.2 Physical Constants of the Hexane Isomers

Molecular Formula	Structural Formula	mp (°C)	bp (°C)[a] (1 atm)	Density[b] (g mL^{-1})	Index of Refraction[a] (n_D 20 °C)
C_6H_{14}	$CH_3CH_2CH_2CH_2CH_3$	–95	68.7	0.6594[20]	1.3748
C_6H_{14}		–153.7	60.3	0.6532[20]	1.3714
C_6H_{14}		–118	63.3	0.6643[20]	1.3765
C_6H_{14}		–128.8	58	0.6616[20]	1.3750
C_6H_{14}		–98	49.7	0.6492[20]	1.3688

a. Unless otherwise indicated, all boiling points are at 1 atm or 760 torr.

b. The superscript indicates the temperature at which the density was measured.

c. The index of refraction is a measure of the ability of the alkane to bend (refract) light rays. The values reported are for light of the D line of the sodium spectrum (n_D).

6. Number of possible constitutional-isomers:

Table 4.3 Number of Alkane Isomers

Molecular Formula	Possible Number of Constitutional Isomers	Molecular Formula	Possible Number of Constitutional Isomers
C_4H_{10}	2	$C_{10}H_{22}$	75
C_5H_{12}	3	$C_{11}H_{24}$	159
C_6H_{14}	5	$C_{15}H_{32}$	4,347
C_7H_{16}	9	$C_{20}H_{42}$	366,319
C_8H_{18}	18	$C_{30}H_{62}$	4,111,846,763
C_9H_{20}	35	$C_{40}H_{82}$	**62,481,801,147,341**

4.3 IUPAC Nomenclature of Alkanes, Alkyl Halides, and Alcohols

1. **Common (trivial) names:** the older names for organic compounds
   1) Acetic acid: *acetum* (Latin: vinegar).
   2) Formic acid: *formicae* (Latin: ants).
2. **IUPAC (International Union of Pure and Applied Chemistry) names:** the formal system of nomenclature for organic compounds

Table 4.4 The Unbranched Alkanes

Number of Carbons (n)	Name	Formula (C_nH_{2n+2})	Number of Carbons (n)	Name	Formula (C_nH_{2n+2})
1	Methane	CH_4	17	Heptadecane	$C_{17}H_{36}$
2	Ethane	C_2H_6	18	Octadecane	$C_{18}H_{38}$
3	Propane	C_3H_8	19	Nonadecane	$C_{19}H_{40}$
4	Butane	C_4H_{10}	20	Eicosane	$C_{20}H_{42}$
5	Pentane	C_5H_{12}	21	Henicosane	$C_{21}H_{44}$
6	Hexane	C_6H_{14}	22	Docosane	$C_{22}H_{46}$
7	Heptane	C_7H_{16}	23	Tricosane	$C_{23}H_{48}$
8	Octane	C_8H_{18}	30	Triacontane	$C_{30}H_{62}$
9	Nonane	C_9H_{20}	31	Hentriacontane	$C_{30}H_{62}$
10	Decane	$C_{10}H_{22}$	40	Tetracontane	$C_{40}H_{82}$
11	Undecane	$C_{11}H_{24}$	50	Pentacontane	$C_{50}H_{102}$
12	Dodecane	$C_{12}H_{26}$	60	Hexacontane	$C_{60}H_{122}$
13	Tridecane	$C_{13}H_{28}$	70	Heptacontane	$C_{70}H_{142}$
14	Tetradecane	$C_{14}H_{30}$	80	Octacontane	$C_{80}H_{162}$
15	Pentadecane	$C_{15}H_{32}$	90	Nonacontane	$C_{90}H_{182}$
16	Hexadecane	$C_{16}H_{34}$	100	Hectane	$C_{100}H_{202}$

Numerical Prefixes Commonly Used in Forming Chemical Names

Numeral	Prefix	Numeral	Prefix	Numeral	Prefix
1/2	hemi-	13	trideca-	28	octacosa-
1	mono-	14	tetradeca-	29	nonacosa-
3/2	sesqui-	15	pentadeca-	30	triaconta-
2	di-, bi-	16	hexadeca-	40	tetraconta-
3	tri-	17	heptadeca-	50	pentaconta-
4	tetra-	18	octadeca-	60	hexaconta-
5	penta-	19	nonadeca-	70	heptaconta-
6	hexa-	20	eicosa-	80	octaconta-
7	hepta-	21	heneicosa-	90	nonaconta-
8	octa-	22	docosa-	100	hecta-
9	nona-, ennea-	23	tricosa-	101	henhecta-
10	deca-	24	tetracosa-	102	dohecta-
11	undeca-, hendeca-	25	pentacosa-	110	decahecta-
12	dodeca-	26	hexacosa-	120	eicosahecta-
		27	heptacosa-	200	dicta-

SI Prefixes

Factor	Prefix	Symbol	Factor	Prefix	Symbol
10^{-18}	atto	a	10	deca	d
10^{-15}	femto	f	10^{2}	hecto	h
10^{-12}	pico	p	10^{3}	kilo	k
10^{-9}	nano	n	10^{6}	mega	M
10^{-6}	micro	μ	10^{9}	giga	G
10^{-3}	milli	m	10^{12}	tera	T
10^{-2}	centi	c	10^{15}	peta	P
10^{-1}	deci	d	10^{18}	exa	E

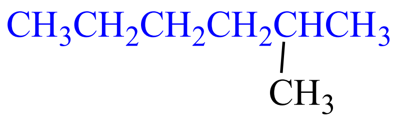
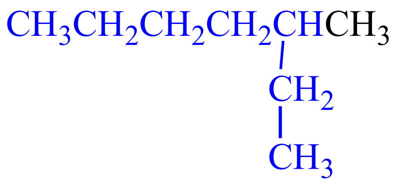
4.3A NOMENCLATURE OF UNBRANCHED ALKYKL GROUPS

1. **Alkyl groups:** **-ane ⇒ -yl** (alkane ⇒ alkyl)

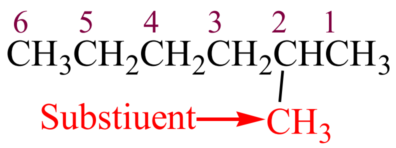
Alkane		Alkyl Group	Abbreviation
CH_3—**H** **Methane**	becomes	CH_3— **Methyl**	Me–
CH_3CH_2—**H** **Ethane**	becomes	CH_3CH_2— **Ethyl**	Et–
$CH_3CH_2CH_2$—**H** **Propane**	becomes	$CH_3CH_2CH_2$— **Propyl**	Pr–
$CH_3CH_2CH_2CH_2$—**H** **Butane**	becomes	$CH_3CH_2CH_2CH_2$— **Butyl**	Bu–

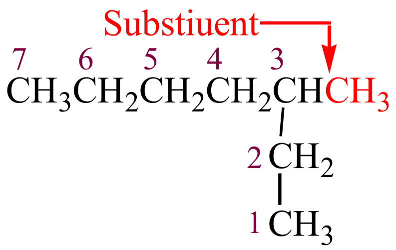
4.3B NOMENCLATURE OF BRANCHED-CHAIN ALKANES

1. **Locate the longest continuous chain** of carbon atoms; this chain determines the **parent name** for the alkane.

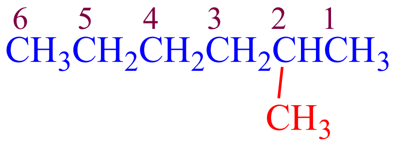



2. **Number the longest chain beginning with the end of the chain nearer the substituent.**

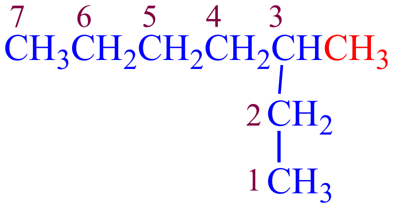




3. **Use the numbers** obtained by application of rule 2 to **designate the location of the substituent group**.



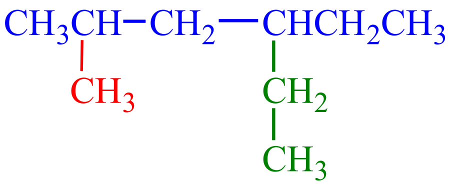
2-Methylhexane



3-Methylheptane

1) The **parent name** is placed **last**; the **substituent group**, preceded by the **number** indicating its **location** on the chain, is placed **first**.

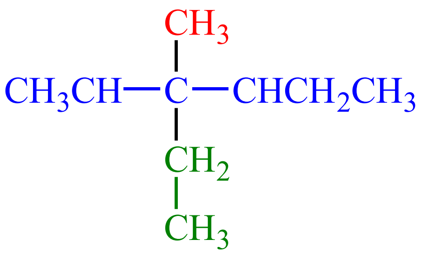
4. When two or more substituents are present, **give each substituent a number corresponding to its location** on the longest chain.



4-Ethyl-2-methylhexane

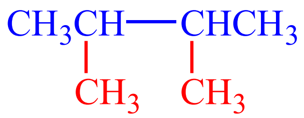
1) The **substituent groups** are listed **alphabetically**.
2) In deciding on **alphabetically** order **disregard** multiplying prefixes such as "**di**" and "**tri**".

5. When two substituents are present on the same carbon, use the number twice.

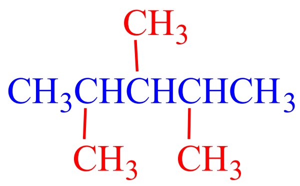


3-Ethyl-3-methylhexane

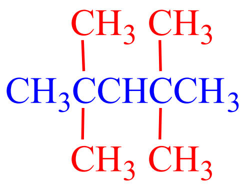
6. When two or more substituents are identical, indicate this by the use of the prefixes **di-**, **tri-**, **tetra-**, and so on.



2,3-Dimethylbutane

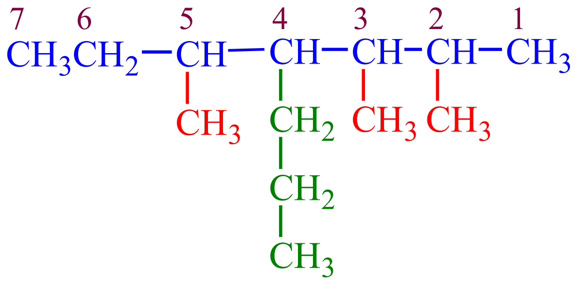


2,3,4-Trimethylpentane



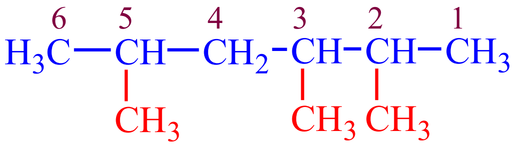
2,2,4,4-Tetramethylpentane

7. When two chains of equal length compete for selection as the parent chain, **choose the chain with the greater number of substituents**.



2,3,5-Trimethyl-4-propylheptane
(four substituents)

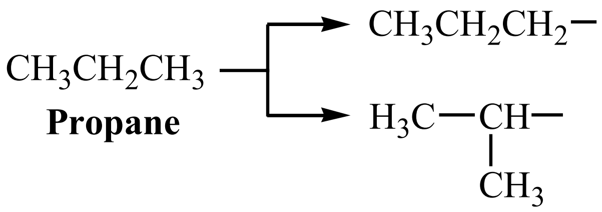
8. When branching first occurs at an equal distance from either end of the longest chain, **choose the name that gives the lower number at the first point of difference**.



2,3,5-Trimethylhexane
(*not* 2,4,5-Trimethylhexane)

4.3C NOMENCLATURE OF BRANCHED ALKYL GROUPS

1. ***Three-Carbon Groups***



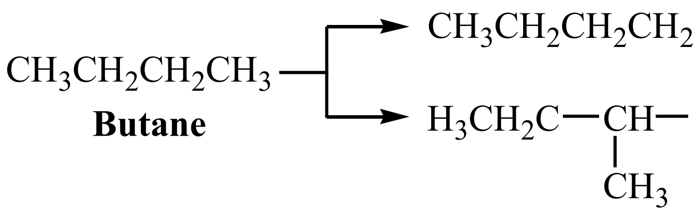
Propyl group

1-Methylethyl or isopropyl group

1) **1-Methylethyl** is the **systematic name**; **isopropyl** is a **common name**.

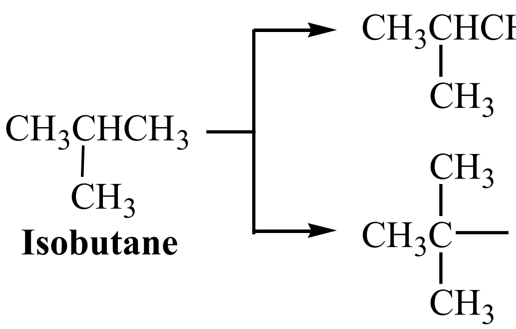
2) ***Numbering always begins at the point where the group is attached to the main chain***.

2. ***Four-Carbon Groups***



Butyl group

1-Methylpropyl or *sec*-butyl group

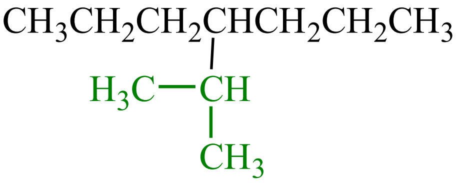


2-Methylpropyl or isobutyl group

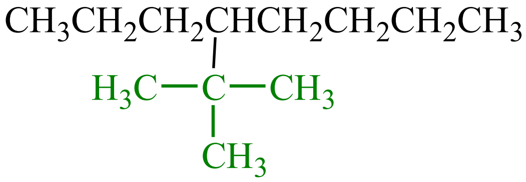
1,1-Dimethylethyl or *tert*-butyl group

1) **4 alkyl groups:** 2 derived from **butane**; 2 derived from **isobutane**.

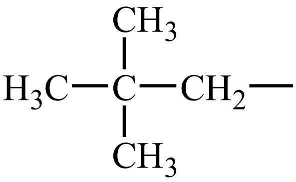
3. Examples:



4-(1-Methylethyl)heptane or 4-isopropylheptane



4-(1,1-Dimethylethyl)octane or 4-*tert*-butyloctane



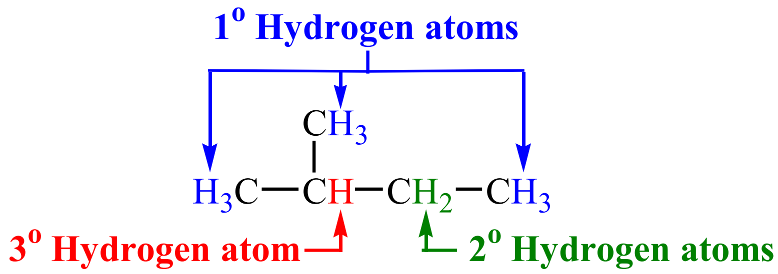
2,2-Dimethylpropyl or neopentyl group

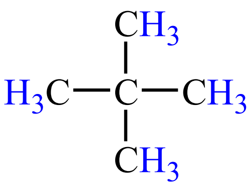
4. The common names **isopropyl**, **isobutyl**, ***sec*-butyl**, ***tert*-butyl** are **approved by the IUPAC** for the unsubstituted groups.
   1) In deciding on **alphabetically** order **disregard** structure-defining prefixes that are written in italics and separated from the name by a hyphen. Thus "***tert*-butyl**" precedes "**ethyl**", but "**ethyl**" precedes "**isobutyl**".

5. The common name **neopentyl group** is **approved by the IUPAC**.

4.3D Classification of Hydrogen Atoms

1. Hydrogen atoms are classified on the basis of the carbon atom to which they are attached.
   1) **Primary** (1°), **secondary** (2°), **tertiary** (3°):





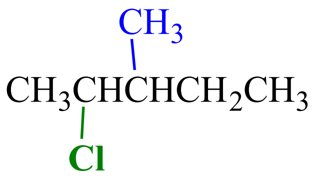
2,2-Dimethylpropane (**neopentane**) has only 1° hydrogen atoms

4.3E Nomenclature of Alkyl Halides

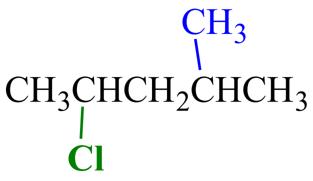
1. **Haloalkanes:**

CH_3CH_2Cl	$CH_3CH_2CH_2F$	$CH_3CHBrCH_3$
Chloroethane	**1-Fluoropropane**	**2-Bromopropane**
Ethyl chloride	***n*-Propyl fluoride**	**Isopropyl bromide**

1) When the parent chain has both a halo and an alkyl substituent attached to it, **number the chain from the end nearer the first substituent**.



2-Chloro-3-methylpentane



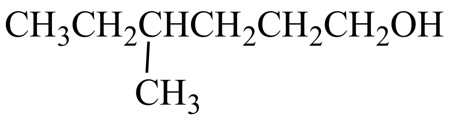
2-Chloro-4-methylpentane

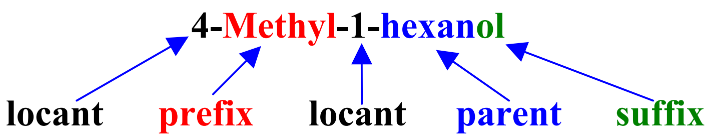
2) **Common names** for simple **haloalkanes** are **accepted** by the **IUPAC** ⇒ **alkyl halides** (***radicofunctional nomenclature***).

$(CH_3)_3CBr$	$CH_3CH(CH_3)CH_2Cl$	$(CH_3)_3CCH_2Br$
2-Bromo-2-methylpropane	**1-Chloro-2-methylpropane**	**1-Bromo-2,2-dimethylpropane**
***tert*-Butyl bromide**	**Isobutyl chloride**	**Neopentyl bromide**

4.3F NOMENCLATURE OF ALCOHOLS

1. IUPAC **substitutive nomenclature:** **locants**, **prefixes**, **parent compound**, and **one suffix**.





1) The ***locant*** **4-** tells that the substituent **methyl** group, named as a ***prefix***, is attached to the ***parent compound*** at C4.
2) The ***parent name*** is **hexane**.
3) An alcohol has the ***suffix*** **-ol**.
4) The ***locant*** **1-** tells that C1 bears the hydroxyl group.
5) In general, **numbering of the chain always begins at the end nearer the group named as a suffix**.

2. IUPAC **substitutive names** for alcohols:

1) Select the **longest continuous carbon chain** ***to which the hydroxyl is directly attached***.

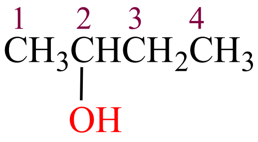
2) Change the name of the **alkane** corresponding to this chain by dropping the final **-e** and adding the ***suffix*** **-ol**.

3) **Number** the longest continuous carbon chain so as to give the carbon atom bearing the hydroxyl group **the lower number**.

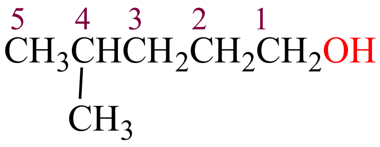
4) Indicate the position of the hydroxyl group by using this number as a locant; indicate the positions of other substituents (as prefixes) by using the numbers corresponding to their positions as locants.

3 2 1
$CH_3CH_2CH_2OH$

1-Propanol



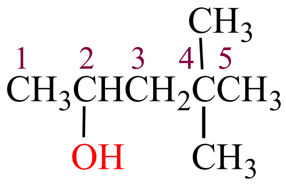
2-Butanol



4-Methyl-1-pentanol
(not 2-methyl-5-pentanol)

3 2 1
$ClCH_2CH_2CH_2OH$

3-Chloro-1-propanol



4,4-Dimethyl-2-pentanol

3. Common **radicalfunctional names** for alcohols:

1) Simple alcohols are often called by ***common names*** that are approved by the IUPAC.

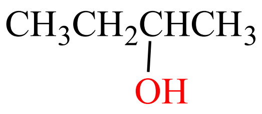
2) *Methyl alcohol*, *ethyl alcohol*, *isopropyl alcohol*, and other examples:

$CH_3CH_2CH_2OH$

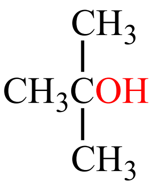
propyl alcohol

$CH_3CH_2CH_2CH_2OH$

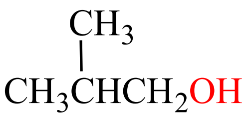
Butyl alcohol



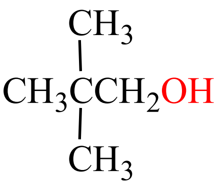
***sec*-Butyl alcohol**



tert-Butyl **alcohol**

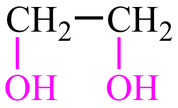
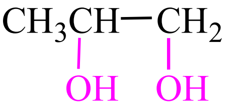
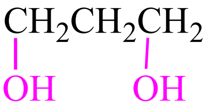


Isobutyl alcohol



Neopentyl alcohol

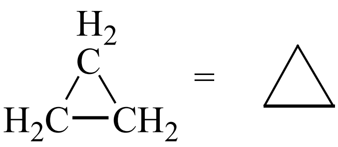
3) Alcohols containing two hydroxyl groups are **commonly** called **gylcols**. In IUPAC **substitutive** system they are named as **diols**.

			
Common	**Ethylene glycol**	**Propylene glycol**	**Trimethylene glycol**
Substitutive	**1,2-Ethanediol**	**1,2-Propanediol**	**1,3-Propanediol**

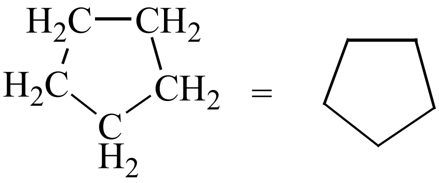
4.4 NOMENCLATURE OF CYCLOALKANES

4.4A MONOCYCLIC COMPOUNDS

1. Cycloalkanes with only one ring:



Cyclopropane

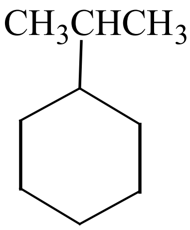


Cyclopentane

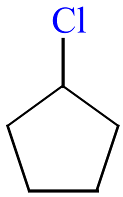
1) Substituted cycloalkanes: ***alkylcycloalkanes, halocycloalkanes, alkylcycloalkanols***

2) Number the ring ***beginning with the substituent first in the alphabet***, and number in the direction that gives the next substituent the **lower number** possible.

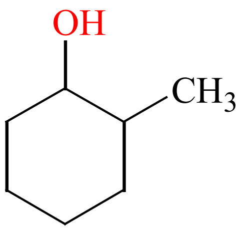
3) When **three or more** substituents are present, begin at the substituent that **leads to the lowest set of locants**.



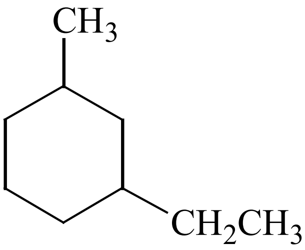
Isopropylcyclohexane



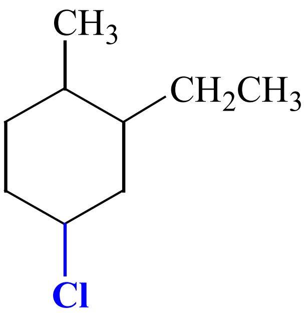
Chlorocyclopentane



2-Methylcyclohexanol

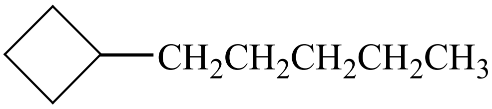


1-Ethyl-3-methylcyclohexane
(not **1-ethyl-5-methylcyclohexane**)

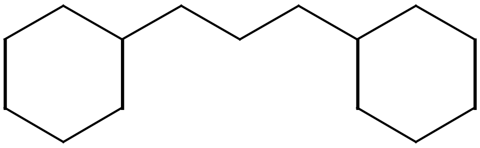


4-Chloro-2-ethyl-1-methylcyclohexane
(not **1-Chloro-3-ethyl-4-methylcyclohexane**)

2. When a single ring system is attached to a single chain with a greater number of carbon atoms, or when more than one ring system is attached to a single chain:



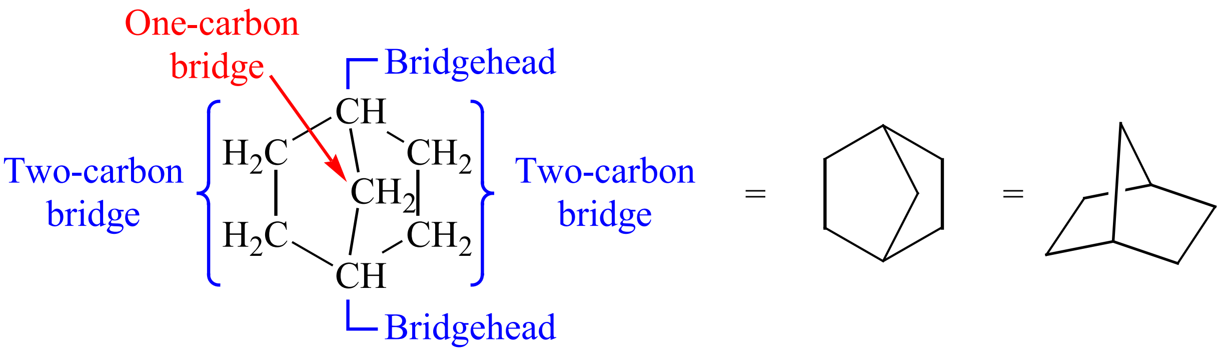
1-Cyclobutylpentane



1,3-Dicyclohexylpropane

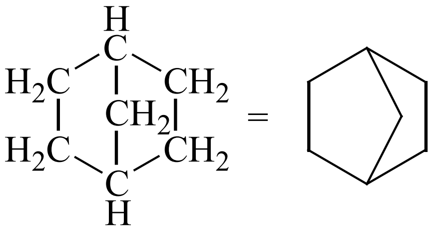
4.4B BICYCLIC COMPOUNDS

1. **Bicycloalkanes:** compounds containing two fused or bridged rings.

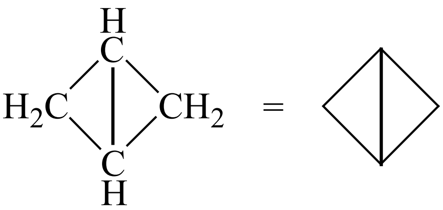


A bicycloheptane

1) The **number of carbon atoms** in **each bridge** is interposed in brackets **in order of decreasing length**.

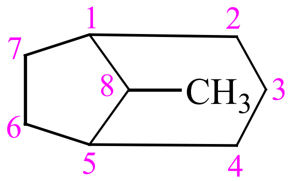


Bicyclo[2.2.1]heptane
(also called **norbornane**)

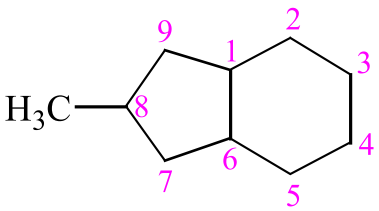


Bicyclo[1.1.0]butane

2) Number the bridged ring system **beginning at one bridgehead**, proceeding **first along the longest bridge** to **the other bridgehead**, then **along the next longest bridge** to **the first bridgehead**.



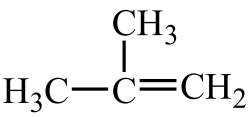
8-Methylbicyclo[3.2.1]octane



8-Methy;bicyclo[4.3.0]nonane

4.5 Nomenclature of Alkenes and Cycloalkenes

1. **Alkene common names:**

	$H_2C{=}CH_2$	$CH_3CH{=}CH_2$	
IUPAC:	**Ethene**	**Propene**	**2-Methylpropene**
Common:	**Ethylene**	**Propylene**	**Isobutylene**

4.5A IUPAC Rules

1. Determine the **parent name** by selecting **the longest chain** that **contains the double bond** and change the ending of the name of the alkane of identical length from **-ane** to **-ene**.

2. **Number the chain** so as to **include both carbon atoms** of the double bond, and begin numbering at **the end of the chain nearer the double bond**. Designate the **location of the double bond** by using **the number of the first atom** of the double bond as a prefix:

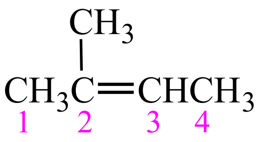
$$\overset{1}{H_2C}{=}\overset{2}{C}H\overset{3}{C}H_2\overset{4}{C}H_3$$

1-Butene (*not* **3-Butene**)

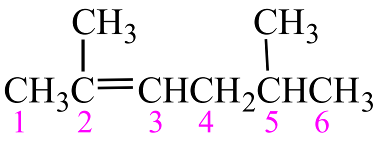
$$\overset{1}{C}H_3\overset{2}{C}H{=}\overset{3}{C}H\overset{4}{C}H_2\overset{5}{C}H_2\overset{6}{C}H_3$$

2-Hexene (*not* **4-hexene**)

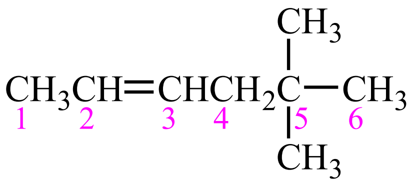
3. Indicate the **locations** of the **substituent groups** by the numbers of the carbon atoms to which they attached.



2-Methyl-2-butene
(*not* **3-methyl-2-butene**)



2,5-Dimethyl-2-hexene
(*not* **2,5-dimethyl-4-hexene**)

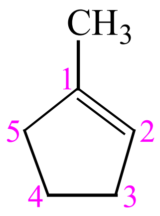


5,5-Dimethyl-2-hexene

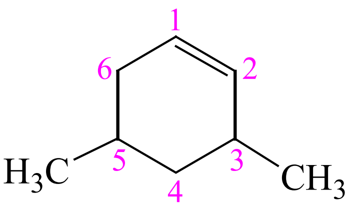
$$\overset{4}{C}H_3\overset{3}{C}H{=}\overset{2}{C}H\overset{1}{C}H_2Cl$$

1-Chloro-2-butene

4. Number substituted cycloalkenes in the way that **gives the carbon atoms of the double bond the 1 and 2 positions** and that also **gives the substituent groups the lower numbers at the first point of difference**.

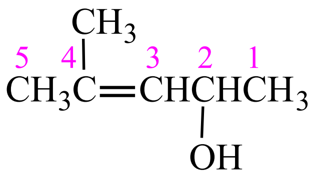


1-Methylcyclopentene
(*not* **2-methylcyclopentene**)

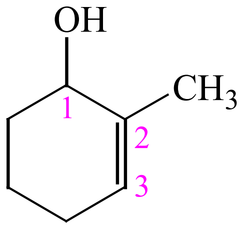


3,5-Dimethylcyclohexene
(*not* **4,6-dimethylcyclohexene**)

5. Name compounds containing a double bond and an alcohol group as **alkenols** (or **cycloalkenols**) and **give the alcohol carbon the lower number**.



4-Methyl-3-penten-2-ol



2-Methyl-2-cyclohexen-1-ol

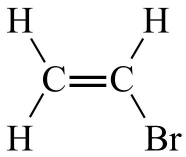
6. The ***vinyl group*** and the ***allyl group***.

$H_2C{=}CH-$

The vinyl group

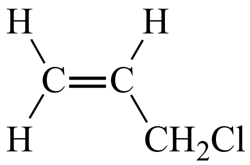
$H_2C{=}CHCH_2-$

The allyl group



Bromoethene or

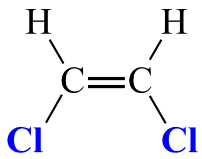
vinyl bromide (common)



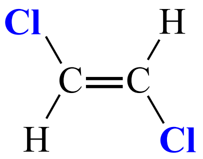
3-Chloropropene or

allyl chloride (common)

7. ***Cis***- and ***trans*-alkenes:**.



***cis*-1,2-Dichloroethene**



***trans*-1,2-Dichloroethene**

4.6 NOMENCLATURE OF ALKYNES

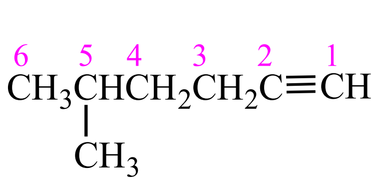
1. Alkynes are named in much the same way as alkenes ⇒ replacing **-ane** to **-yne**.

   1) The chain is numbered to give the carbon atoms of the triple bond **the lower possible numbers**.

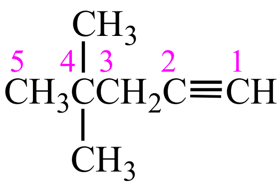
2) The **lower number** of the two carbon atoms of the triple bond is used to designate the location of the triple bond.

3) Where there is a choice **the double bond is given the lower number**.

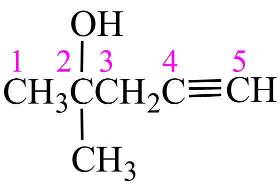
$H-C\equiv C-H$	$CH_3CH_2C\equiv CCH_3$	$H-C\equiv CCH_2CH=CH_2$
Ethyne or **acetylene**	**2-Pentyne**	**1-Penten-4-yne**
$\overset{3}{Cl}H_2\overset{2}{C}\overset{}{C}\equiv \overset{1}{C}H$ (numbering 3 2 1)	$H_3CC\equiv CCH_2Cl$ (numbering 4 3 2 1)	$HC\equiv CCH_2CH_2OH$ (numbering 4 3 2 1)
3-Chloropropyne	**1-Chloro-2-butyne**	**3-Butyn-1-ol**



5-Methyl-1-hexyne



4,4-Dimethyl-1-pentyne



2-Methyl-4-pentyn-2-ol

2. **Terminal alkynes:**

A terminal alkyne

1) ***Alkynide ion*** (***acetylide ion***):

$R-C\equiv C:^-$

An alkynide ion (an acetylide ion)

$CH_3C\equiv C:^-$

The propynide ion

4.7 Physical Properties of Alkanes and Cycloalkanes

1. A series of compounds, where each member differs from the next member by a constant unit, is called a **homologous series**. Members of a homologous series are called **homologs**.

1) At room temperature (rt, 25 °C) and 1 atm pressure, the **C_1-C_4** unbranched

alkanes are **gases**; the **C_5-C_{17}** unbranched alkanes are **liquids**; the unbranched alkanes with **18 or more carbon atoms** are **solids**.

4.7A BOILING POINTS

1. The boiling points of the unbranched alkanes show a regular increase with increasing molecular weight.

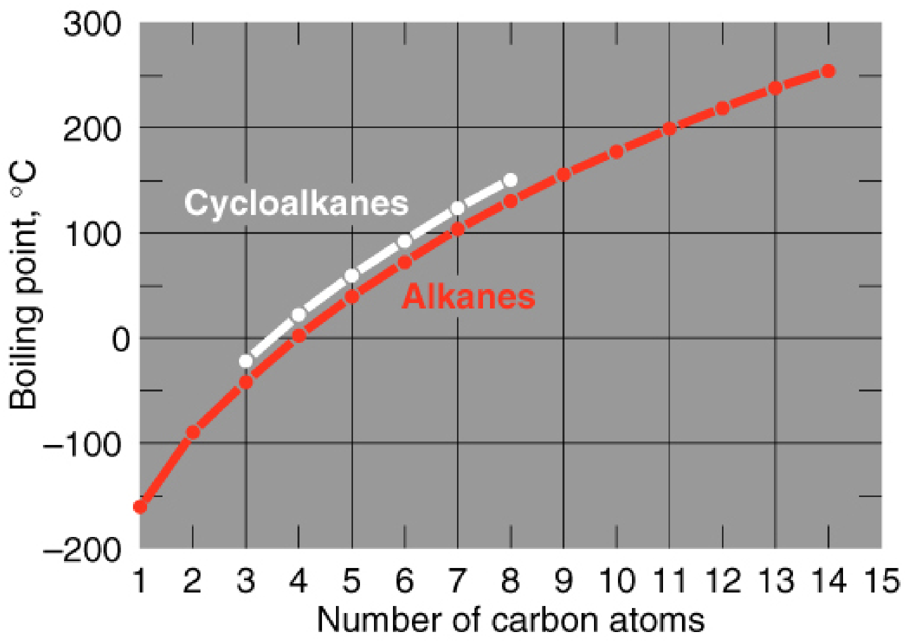


Figure 4.3 Boiling points of unbranched alkanes (in red) and cycloalkanes (in white).

2. **Branching** of the alkane chain **lowers** the **boiling point** (**Table 4.2**).
   1) Boiling points of C_6H_{14}: hexane (68.7 °C); 2-methylpentane (60.3 °C); 3-methylpentane (63.3 °C); 2,3-dimethylbutane (58 °C); 2,2-dimethylbutane (49.7 °C).

3. As the **molecular weight** of unbranched alkanes **increases**, so too does the **molecular size**, and even more importantly **molecular surface areas**.
   1) **Increasing surface area** ⇒ **increasing** the **van der Waals forces** between molecules ⇒ **more energy** (a higher temperature) is required to **separate** molecules from one another and produce **boiling**.

4. **Chain branching** makes a molecule **more compact**, **reducing the surface area**

and with it **the strength** of the **van der Waals forces** operating between it and adjacent molecules ⇒ **lowering the boiling**.

4.7B Melting Points

1. There is an alteration as one progresses from an unbranched alkane with an even number of carbon atoms to the next one with an odd number of carbon atoms.
   1) Melting points: ethane (–183 °C); propane (–188 °C); butane (–138 °C); pentane (–130 °C).

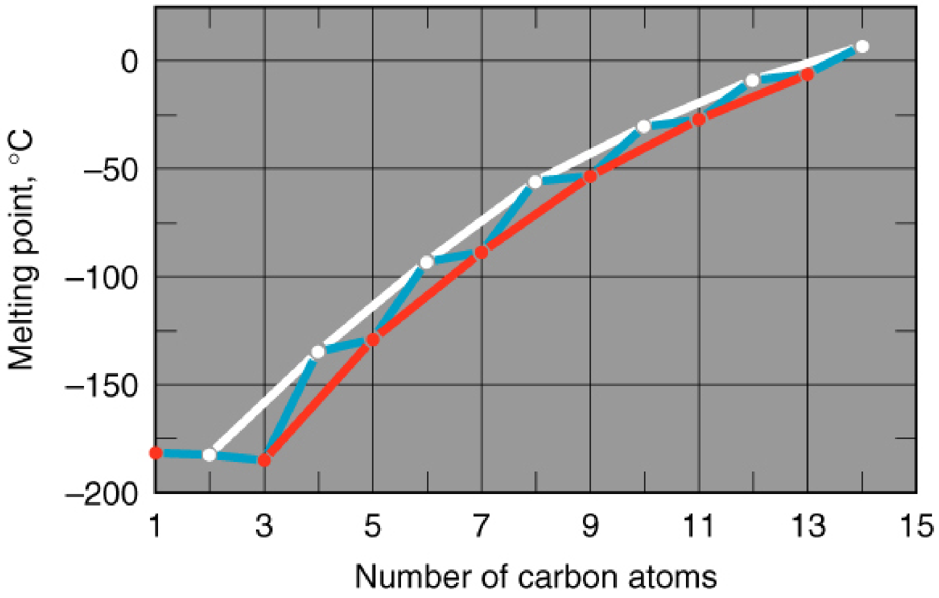
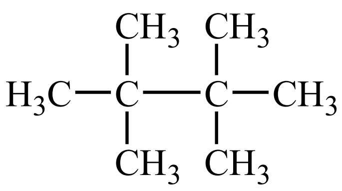


Figure 4.4 Melting points of unbranched alkanes.

2. **X-ray diffraction** studies have revealed that **alkane chains** with an **even number** of carbon atoms **pack more closely** in the crystalline state ⇒ **attractive forces between individual chains are greater and melting points are higher**.
3. **Branching** produces **highly symmetric structures** results in **abnormally high melting points**.
   1) 2,2,3,3,-Tetramethylbutane (mp 100.7 °C); (bp 106.3 °C).



2,2,3,3,-Tetramethylbutane

4.7C Density

1. The alkanes and cycloalkanes are the least dense of all groups of organic compounds.

Table 4.5 Physical Constants of Cycloalkanes

Number of Carbon Atoms	Name	bp (°C) (1 atm)	mp (°C)	Density d^{20} (g mL^{-1})	Refractive Index (n_D^{20})
3	Cyclopropane	–33	–126.6	——	——
4	Cyclobutane	13	–90	——	1.4260
5	Cyclopentane	49	–94	0.751	1.4064
6	Cyclohexane	81	6.5	0.779	1.4266
7	Cycloheptane	118.5	–12	0.811	1.4449
8	Cyclooctane	149	13.5	0.834	——

4.7D Solubility

1. Alkanes and cycloalkanes are almost **totally insoluble in water** because of their **very low polarity** and their **inability to form hydrogen bonds**.
   1) Liquid alkanes and cycloalkanes are soluble in one another, and they generally dissolve in solvents of low polarity.

4.8 Sigma Bonds and Bond Rotation

1. **Conformations:** the **temporary molecular shapes** that result from **rotations of groups** about **single bonds**.
2. **Conformational analysis:** the analysis of the **energy changes** that a molecule undergoes as **groups** rotate about **single bonds**.

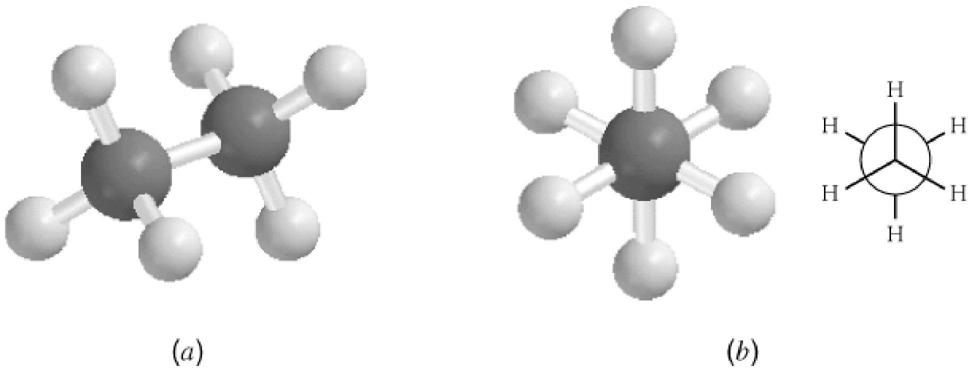
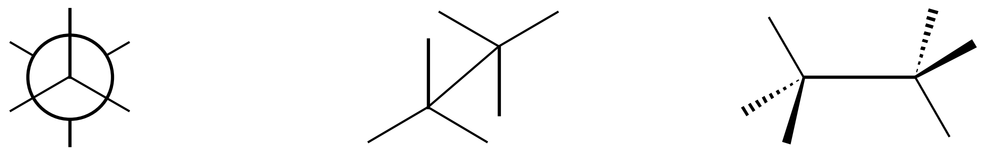


Figure 4.5 a) The staggered conformation of ethane. b) The Newman projection formula for the staggered conformation.

3. **Staggered conformation:** allows the **maximum separation** of the electron pairs of the six C—H bonds ⇒ has the **lowest energy** ⇒ **most stable** conformation.

4. **Newman projection formula:**

5. **Sawhorse formula:**



Newman projection formula **Sawhorse formula**

The hydrogen atoms have been omitted for clarity.

5. **Eclipsed conformation: maximum repulsive interaction** between the electron pairs of the six C—H bonds ⇒ has the **highest energy** ⇒ **least stable** conformation.

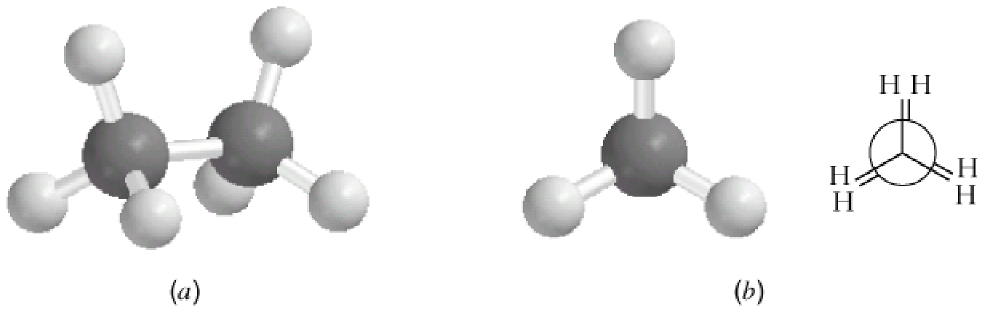


Figure 4.6 The eclipsed conformation of ethane. b) The Newman projection formula for the eclipsed conformation.

5. **Torsional barrier:** the energy barrier to rotation of a single bond.

1) In ethane the difference in energy between the staggered and eclipsed

conformations is 12 kJ mol^{-1} (2.87 kcal mol^{-1}).

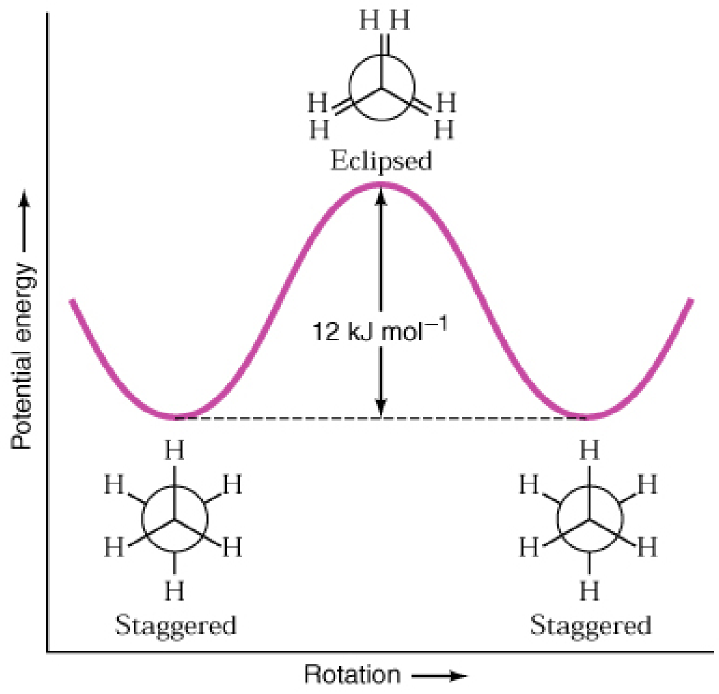


Figure 4.7 Potential energy changes that accompany rotation of groups about the carbon-carbon bond of ethane.

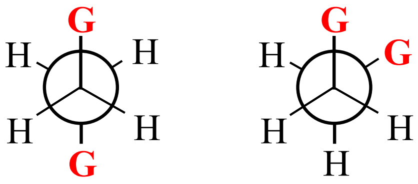
2) Unless the temperature is extremely low (−250 °C), **many** ethane molecules (at any given moment) will have **enough energy** to surmount this barrier.

3) An ethane molecule will spend **most of its time in the lowest energy, staggered conformation**, or in a conformation very close to being staggered. Many times every second, it will acquire **enough energy** through collisions with other molecules to surmount the torsional barrier and will rotate through an **eclipsed conformation**.

4) In terms of a large number of ethane molecules, **most of the molecules** (at any given moment) will be in **staggered** or **nearly staggered conformations**.

6. Substituted ethanes, $\mathbf{G}CH_2CH_2\mathbf{G}$ (**G** is a group or atom other than hydrogen):

1) The barriers to rotation are **far too small** to allow **isolation** of the different **staggered conformations** or **conformers**, even at temperatures considerably below rt.

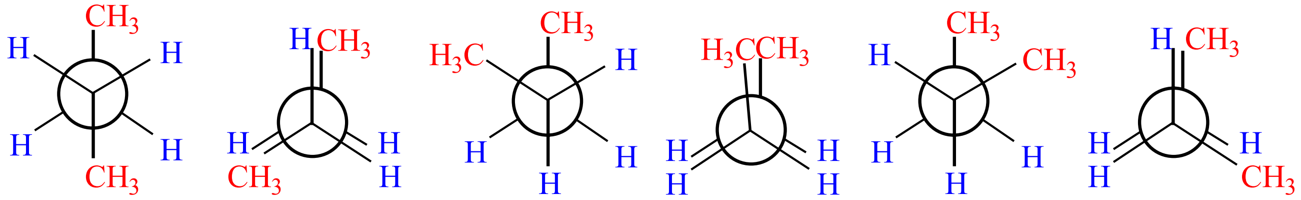


These conformers cannot be isolated except at extremely low temperatures.

4.9 Conformational Analysis of Butane

4.9A A Conformational analysis of Butane

1. Ethane has a **slight barrier** to free **rotation** about the C—C single bond.
   1) This barrier (**torsional strain**) causes the **potential energy** of the ethane molecule to rise to a **maximum** when rotation brings the hydrogen atoms into an eclipsed conformation.
2. Important conformations of butane **I – VI**:



I	II	III	IV	V	VI
An anti conformation	**An eclipsed conformation**	**A gauche conformation**	**An eclipsed conformation**	**A gauche conformation**	**An eclipsed conformation**

   1) The **anti conformation** (**I**)**: does not have torsional strain** ⇒ **most stable**.
   2) The **gauche conformations** (**III** and **V**)**:** the two methyl groups are **close enough to each other** ⇒ the van der Waals forces between them are **repulsive** ⇒ the **torsional strain** is 3.8 kJ mol^{-1} (0.91 kcal mol^{-1}).
   3) The **eclipsed conformation** (**II**, **IV**, and **VI**)**: energy maxima** ⇒ **II**, and **IV** have **torsional strain** and **van der Waals repulsions** arising from the eclipsed methyl group and hydrogen atoms; **VI** has the greatest energy due to the large **van der Waals repulsion force** arising from the eclipsed methyl groups.

4) The **energy barriers** are still too small to **permit isolation** of the **gauche** and **anti conformations** at normal temperatures.

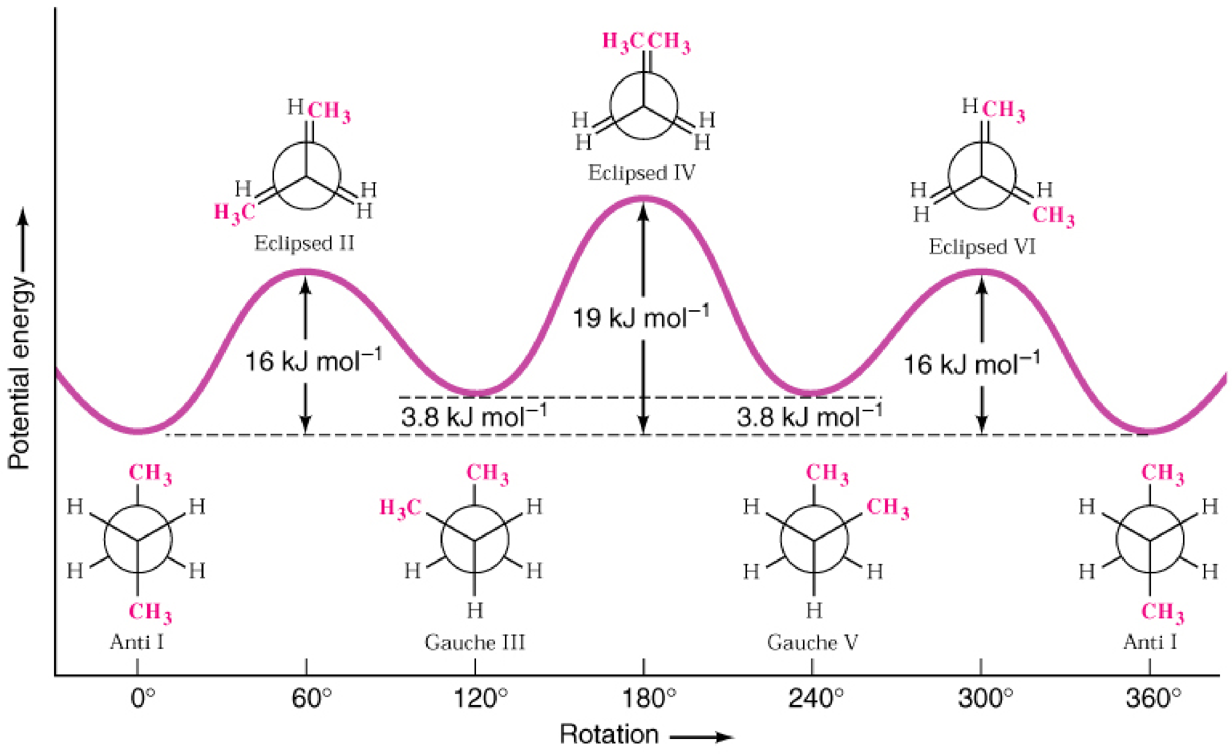


Figure 4.8 Energy changes that arise from rotation about the C2–C3 bond of butane.

3. van der Waals forces can be ***attractive*** or ***repulsive***:

1) **Attraction** or **repulsion** depends of the **distance** that separates the two groups.

2) Momentarily unsymmetrical distribution of electrons in one group **induces** an **opposite polarity** in the other ⇒ when the **opposite charges** are in **closet proximimity** lead to **attraction** between them.

3) The **attraction** increases to a **maximum** as the **internuclear distance** of the two groups **decreases** ⇒ The **internuclear distance** is equal to the **sum** of ***van der Waals radii*** of the two groups.

4) The van der Waals radius is a measure of its ***size***.

5) If the groups are brought still closer —— closer than the **sum** of ***van der Waals radii*** —— the interaction between them becomes **repulsive** ⇒ Their **electron clouds begin to penetrate each other**, and **strong electron-electron interactions** begin to occur.

4.10 THE RELATIVE STABILITIES OF CYCLOALKANES: RING STRAIN

1. **Ring strain:** the **instability** of cycloalkanes due to their **cyclic structures**.⇒ **angle strain** and **torsional strain**.

4.10A HEATS OF COMBUSTION

1. **Heat of combustion:** the **enthalpy change** for the complete oxidation of a compound ⇒ for a hydrocarbon means converting it to $\mathbf{CO_2}$ and **water**.

   1) For methane, the heat of combustion is –803 kJ mol^{-1} (–191.9 kcal mol^{-1}):

$$CH_4 + 2\ O_2 \longrightarrow CO_2 + 2\ H_2O \qquad \Delta H° = -803\ \text{kJ mol}^{-1}$$

   2) Heat of combustion can be used to measure **relative stability** of **isomers**.

$$\underset{(\mathbf{C_4H_{10}},\ \text{butane})}{CH_3CH_2CH_2CH_3} + 6\frac{1}{2}\ O_2 \longrightarrow 4\ CO_2 + 5\ H_2O \qquad \Delta H° = -2877\ \text{kJ mol}^{-1}$$
$$-687.6\ \text{kcal mol}^{-1}$$

$$\underset{(\mathbf{C_4H_{10}},\ \text{isobutane})}{CH_3\underset{|\atop CH_3}{C}HCH_3} + 6\frac{1}{2}\ O_2 \longrightarrow 4\ CO_2 + 5\ H_2O \qquad \Delta H° = -2868\ \text{kJ mol}^{-1}$$
$$-685.5\ \text{kcal mol}^{-1}$$

   i) Since butane **liberates more heat** (9 kJ mol^{-1} = 2.15 kcal mol^{-1}) on combustion than isobutene, it must contain **relative more potential energy**.

   ii) Isobutane must be ***more stable***.

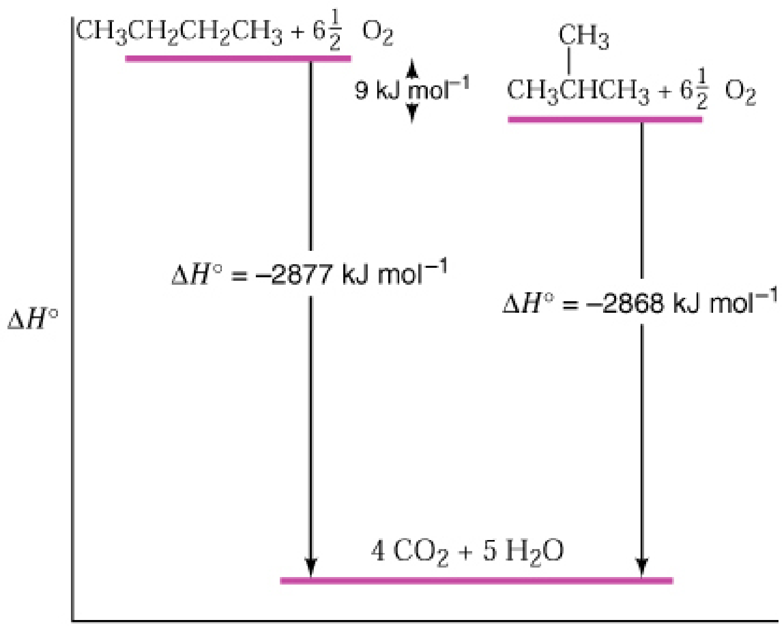


Figure 4.9 Heats of combustion show that isobutene is more stable than butane by 9 kJ mol^{-1}.

4.10B HEATS OF COMBUSTION OF CYCLOALKANES

$$(CH_2)_n + \frac{3}{2} n\ O_2 \longrightarrow n\ CO_2 + n\ H_2O + \text{heat}$$

Table 4.6 Heats of Combustion and ring Strain of Cycloalkanes

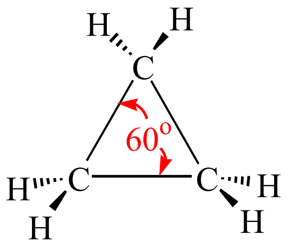
Cycloalkane $(CH_2)_n$	*n*	Heat of Combustion (kJ mol^{-1})	Heat of Combustion per CH_2 Group (kJ mol^{-1})		Ring Strain (kJ mol^{-1})	
Cyclopropane	3	2091	697.0	(166.59)[a]	115	(27.49)[a]
Cyclobutane	4	2744	686.0	(163.96)[a]	109	(26.05)[a]
Cyclopentane	5	3320	664.0	(158.70)[a]	27	(6.45)[a]
Cyclohexane	6	3952	658.7	(157.43)[a]	0	(0)[a]
Cycloheptane	7	4637	662.4	(158.32)[a]	27	(6.45)[a]
Cyclooctane	8	5310	663.8	(158.65)[a]	42	(10.04)[a]
Cyclononane	9	5981	664.6	(158.84)[a]	54	(12.91)[a]
Cyclodecane	10	6636	663.6	(158.60)[a]	50	(11.95)[a]
Cyclopentadecane	15	9885	659.0	(157.50)[a]	6	(1.43)[a]
Unbranched alkane			658.6	(157.39)[a]	——	

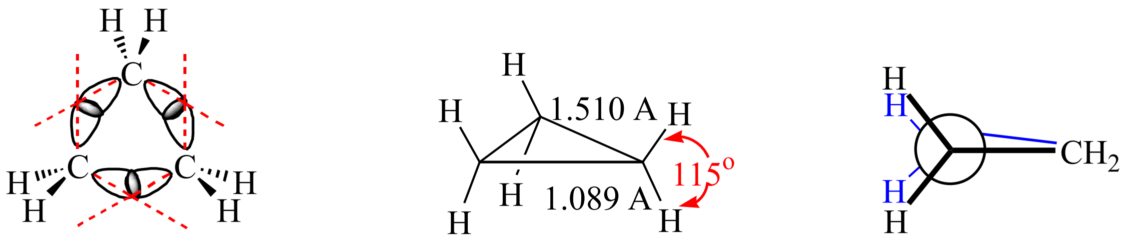
a. In kcal mol^{-1}.

1. Cyclohexane has the **lowest** heat of combustion per CH_2 group (658.7 kJ mol^{-1}).⇒ the same as unbranched alkanes (having no ring strain) ⇒ cyclohexane has **no ring strain**.
2. Cycloporpane has the **greatest** heat of combustion per CH_2 group (697 kJ mol^{-1}) ⇒ cycloporpane has the **greatest ring strain** (115 kJ mol^{-1}) ⇒ cyclopropane contains the **greatest amount of potential energy** per CH_2 group.
   1) The **more ring strain** a molecule possesses, the **more potential energy** it has and the **less stable** it is.
3. Cyclobutane has the **second largest** heat of combustion per CH_2 group (686.0 kJ mol^{-1}) ⇒ cyclobutane has the second largest **ring strain** (109 kJ mol^{-1}).
4. Cyclopentane and cycloheptane have about the same **modest** amount of **ring strain** (27 kJ mol^{-1}).

4.11 THE ORIGIN OF RING STRAIN IN CYCLOPROPANE AND CYCLOBUTANE: ANGLE STRAIN AND TORSIONAL STRAIN

1. The carbon atoms of alkanes are sp^3 hybridized ⇒ the bond angle is 109.5°.
   1) The internal angle of cyclopropane is 60° and departs from the ideal value by a very large amout — by 49.5°.



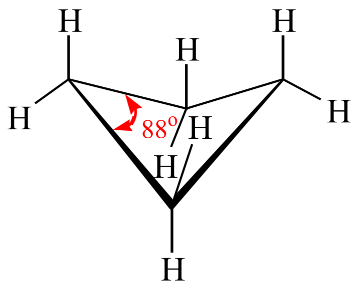


(a) (b) (c)

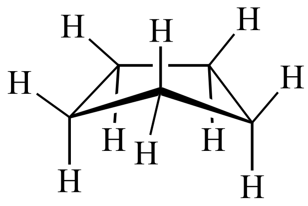
Figure 4.10 (a) Orbital overlap in the carbon-carbon bonds of cyclopropane cannot

occur perfectly end-on. This leads to weaker "bent" bonds and to angle strain. (b) Bond distances and angles in cyclopropane. (c) A Newman projection formula as viewed along one carbon-carbon bond shows the eclipsed hydrogens (Viewing along either of the other two bonds would show the same pictures.)

2. **Angle strain:** the potential energy rise resulted from compression of the internal angle of a cycloalkane from normal sp^3-hybridized carbon angle.
   1) The sp^3 orbitals of the carbon atoms cannot overlap as effectively as they do in alkane (where perfect **end-on overlap** is possible).



(a)



(b)

Figure 4.11 (a) The "folded" or "bent" conformation of cyclobutane. (b) The "bent" or "envelop" form of cyclopentane. In this structure the front carbon atom is bent upward. In actuality, the molecule is flexible and shifts conformations constantly

   2) The **C—C bonds** of cyclopropane are "**bent**" ⇒ **orbital overlap is less effectively** (the orbitals used for these bonds are not purely sp^3, they contain more p character) ⇒ the **C—C bonds** of cyclopropane are **weaker** ⇒ cyclopropane has greater potential energy.
   3) The hydrogen atoms of the cyclopropane ring are all **eclipsed** ⇒ cyclopropane has **torsional strain**.
   4) The internal angles of cyclobutane are 88° ⇒ considerably **angle strain**.
   5) The cyclobutane ring is not plannar but is slightly "**folded**" ⇒ considerably larger **torsional strain** can be relieved by sacrificing a little bit of **angle strain**.

4.11A CYCLOPENTANE

1. Cyclopentane has **little** torsional strain and angle strain.

   1) The internal angles are 108° ⇒ very **little** angle strain **if it was planar** ⇒ considerably **torsional strain**.

   2) Cyclopentane assumes a slightly bent conformation ⇒ **relieves** some of the **torsional strain**.

   3) Cyclopentane is **flexible** and shifts rapidly form one conformation to another.

4.12 CONFORMATIONS OF CYCLOHEXANE

1. The **most stable** conformation of the cyclohexane ring is the "**chair**" conformation:

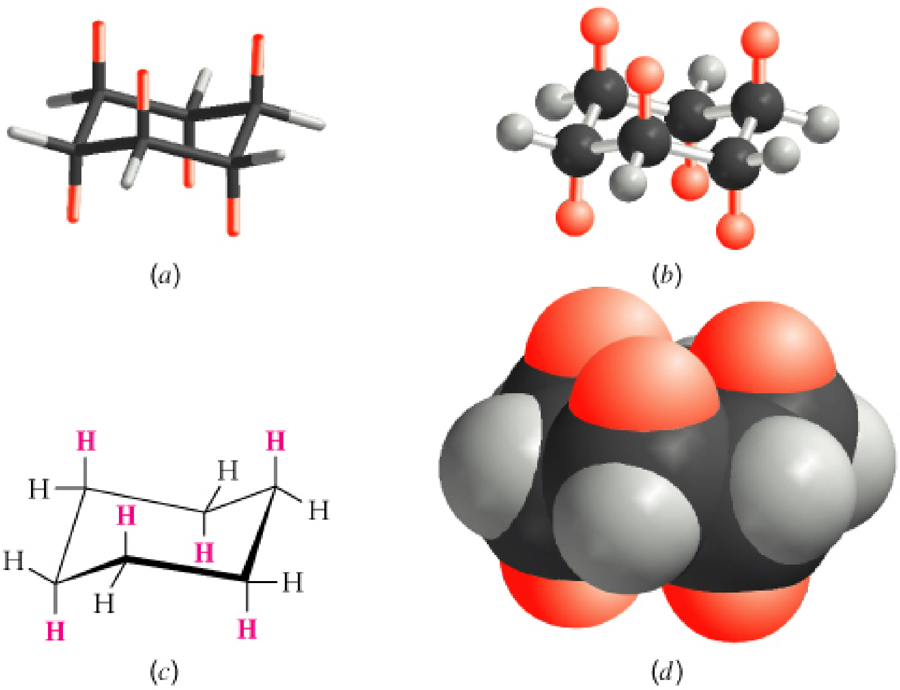


Figure 4.12 Representations of the chair conformation of cyclohexane: (a) Carbon skeleton only; (b) Carbon and hydrogen atoms; (c) Line drawing; (d) Space-filling model of cyclohexane. Notice that there are two types of hydrogen substituents--those that project obviously up or down (shown in red) and those that lie around the perimeter of the ring in more subtle up or down orientations (shown in black or gray). We shall discuss this further in Section 4.13.

   1) The **C—C** bond angles are all 109.5° ⇒ **free** of angle strain.

   2) Chair cyclohexane is **free** of torsional strain:

i) When viewed along any **C—C** bond, the atoms are seen to be perfectly **staggered**.

ii) The hydrogen atoms at **opposite corners** (C1 and C4) of the cyclohexane ring are **maximally separated**.

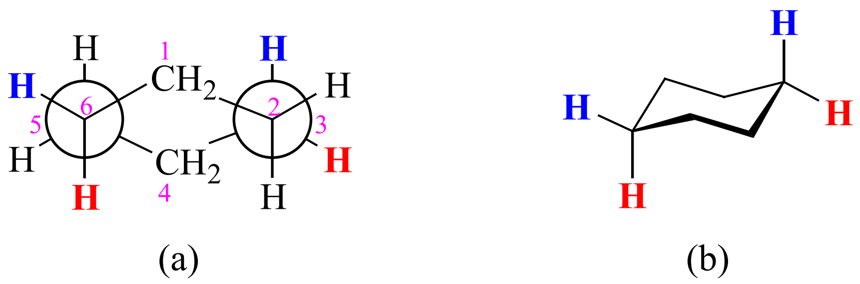


Figure 4.13 (a) A Newman projection of the chair conformation of cyclohexane. (Comparisons with an actual molecular model will make this formulation clearer and will show that similar staggered arrangements are seen when other carbon-carbon bonds are chosen for sighting.) (b) Illustration of large separation between hydrogen atoms at opposite corners of the ring (designated C1 and C4) when the ring is in the chair conformation.

2. **Boat conformation** of cyclohexane:

1) Boat conformation of cyclohexane is **free** of angle strain.

2) Boat cyclohexane has **torsional strain** and **flagpole interaction**.

i) When viewed along the **C—C** bond on either side, the atoms are found to be **eclipsed** ⇒ considerable **torsional strain**.

ii) The hydrogen atoms at **opposite corners** (C1 and C4) of the cyclohexane ring are **close enough** to cause van der Waals **repulsion** ⇒ **flagpole interaction**.

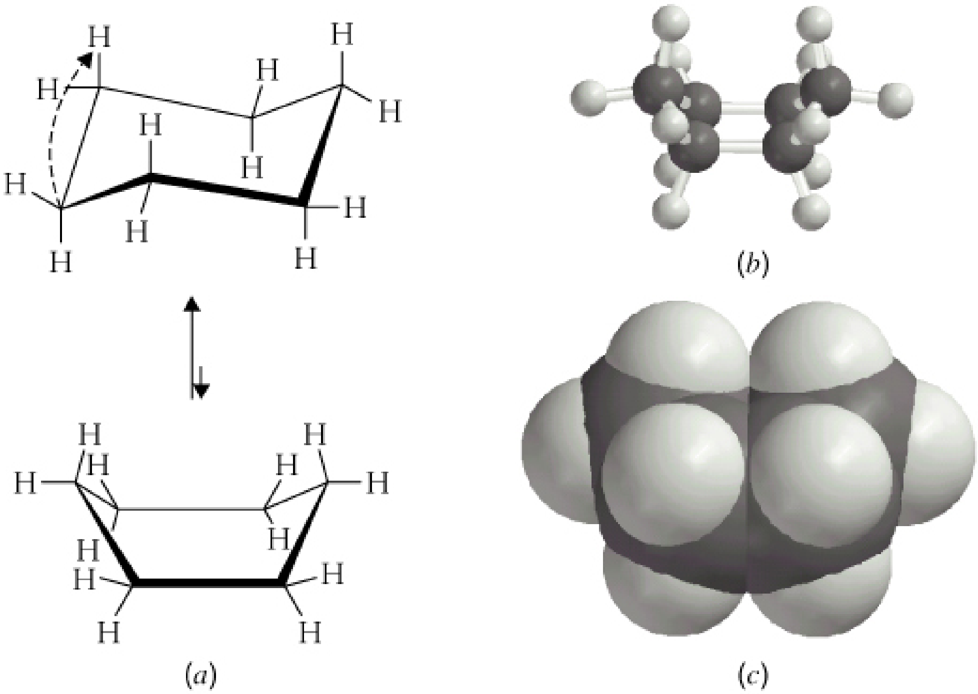


Figure 4.14 **(a) The boat conformation of cyclohexane is formed by "flipping" one end of the chair form up (or down). This flip requires only rotations about carbon-carbon single bonds. (b) Ball-and-stick model of the boat conformation. (c) A space-filling model.**

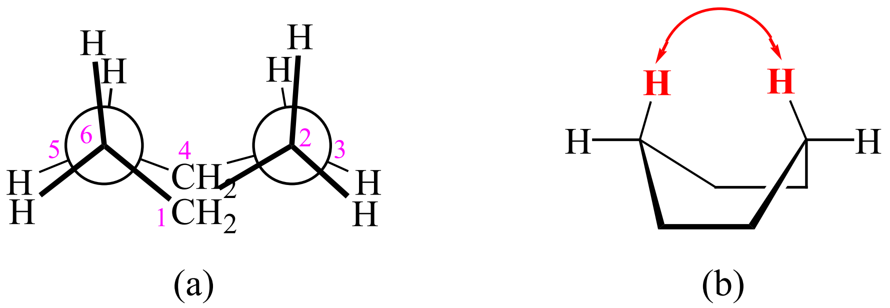


Figure 4.15 **(a) Illustration of the eclipsed conformation of the boat conformation of cyclohexane. (b) Flagpole interaction of the C1 and C4 hydrogen atoms of the boat conformation.**

3. The chair conformation is much more **rigid** than the boat conformation.
   1) The boat conformation is quite flexible.
   2) By flexing to the **twist conformation**, the boat conformation can **relieve** some of its **torsional strain** and **reduce** the **flagpole interactions**.

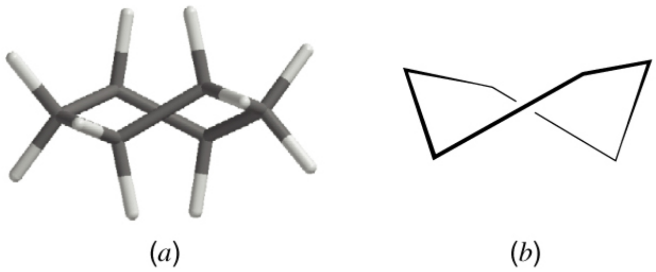


Figure 4.16 (a) Carbon skeleton and (b) line drawing of the twist conformation of cyclohexane.

4. The **energy barrier** between the chair, boat, and twist conformations of cyclohexane are **low** enough to make **separation of the conformers impossible** at room temperature.

   1) **Because of the greater stability of the chair, more than 99% of the molecules are estimated to be in a chair conformation at any given moment**.

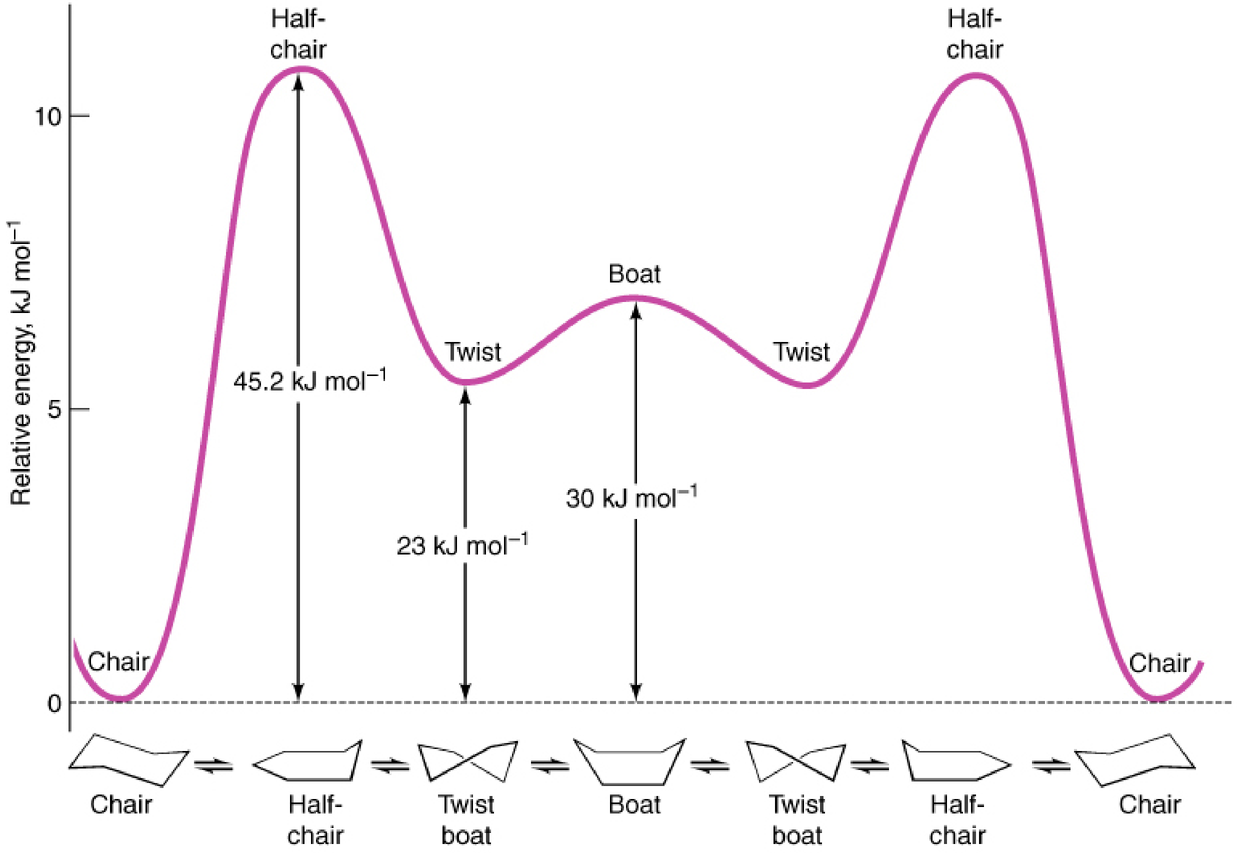


Figure 4.17 The relative energies of the various conformations of cyclohexane. The positions of maximum energy are conformations called half-chair conformations, in which the carbon atoms of one end of the ring have become coplanar.

Table 4-1 Energy costs for interactions in alkane conformers

Interaction	*Cause*	*Energy cost* (kcal/mol)	(kJ/mol)
H–H eclipsed	Torsional strain	1.0	4
H–CH_3 eclipsed	Mostly torsional strain	1.4	6
CH_3–CH_3 eclipsed	Torsional plus steric strain	2.5	11
CH_3–CH_3 gauche	Steric strain	0.9	4

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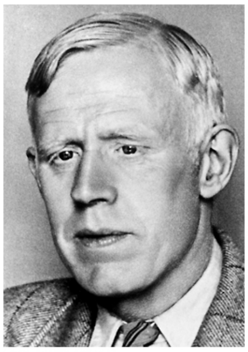
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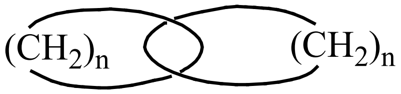
Sir Derek H. R. Barton (1918-1998, formerly Distinguished Professor of Chemistry at Texas A&M University) and Odd Hassell (1897-1981, formerly Chair of Physical Chemistry of Oslo University) shared the Nobel prize in 1969 "for developing and applying the principles of conformation in chemistry." Their work led to fundamental understanding of not only the conformations of cyclohexane rings, but also the structures of steroids (Section 23.4) and other compounds containing cyclohexane rings.

4.12A Conformation of Higher Cycloalkanes

1. Cycloheptane, cyclooctane, and cyclononane and other higher cycloalkanes exist in **nonplanar** conformations.
2. Torsional strain and van der Waals repulsions between hydrogen atoms across rings (**transannular strain**) cause the small instabilities of these higher cycloalkanes.
3. The most stable conformation of cyclodecane has a C−C−C bond angles of 117°.
   1) It has some angle strain.
   2) It allows the molecules to expand and thereby minimize unfavorable repulsions between hydrogen atoms across the ring.



A catenane (*n* ≥ 18)

4.13 Substituted Cyclohexanes: Axial and Equatorial Hydrogen Atoms

1. The six-membered ring is the most common ring found among nature's organic molecules.
2. The chair conformation of cyclohexane is the most stable one and that it is the predominant conformation of the molecules in a sample of cyclohexane.
   1) **Equatorial** hydrogens: the hydrogen atoms lie around the perimeter of the ring of carbon atoms.
   2) **Axial** hydrogens: the hydrogen atoms orient in a direction that is generally perpendicular to the average of the ring of carbon atoms.

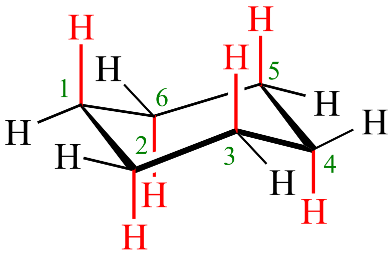


Figure 4.18 The chair conformation of cyclohexane. The axial hydrogen atoms are shown in color.

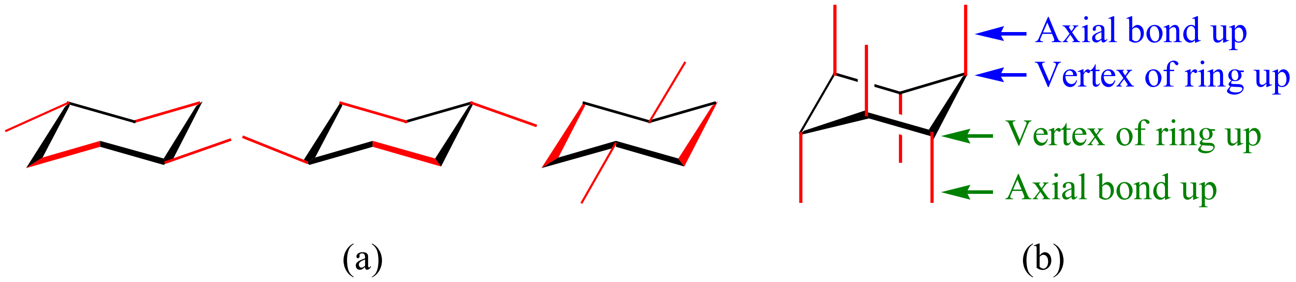
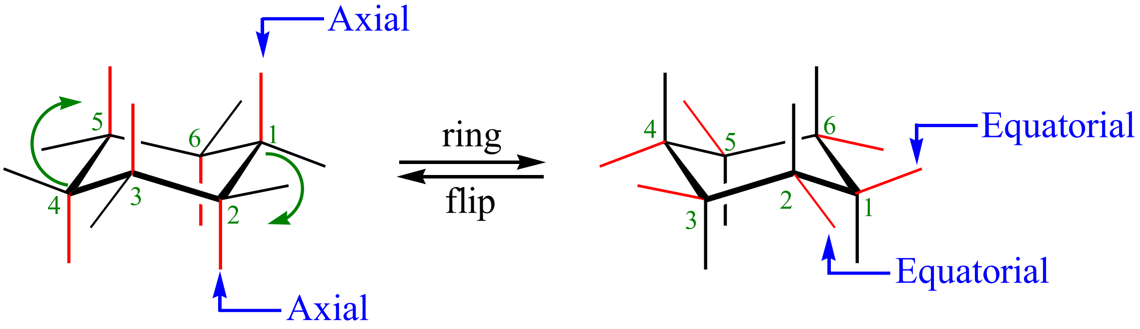


Figure 4.19 (a) Sets of parallel lines that constitute the ring and equatorial C–H bonds of the chair conformation. (b) The axial bonds are all vertical. When the vertex of the ring points up, the axial bond is up and vice versa.

3) **Ring flip:**

i) The cylohexane ring rapidly flips back and forth between two ***equivalent*** chair conformation via partial rotations of C—C bonds.

ii) **When the ring flips, all of the bonds that were axial become equatorial and vice versa**.



3. The most stable conformation of substituted chclohexanes:

1) There are two possible chair conformations of methylcyclohexane.

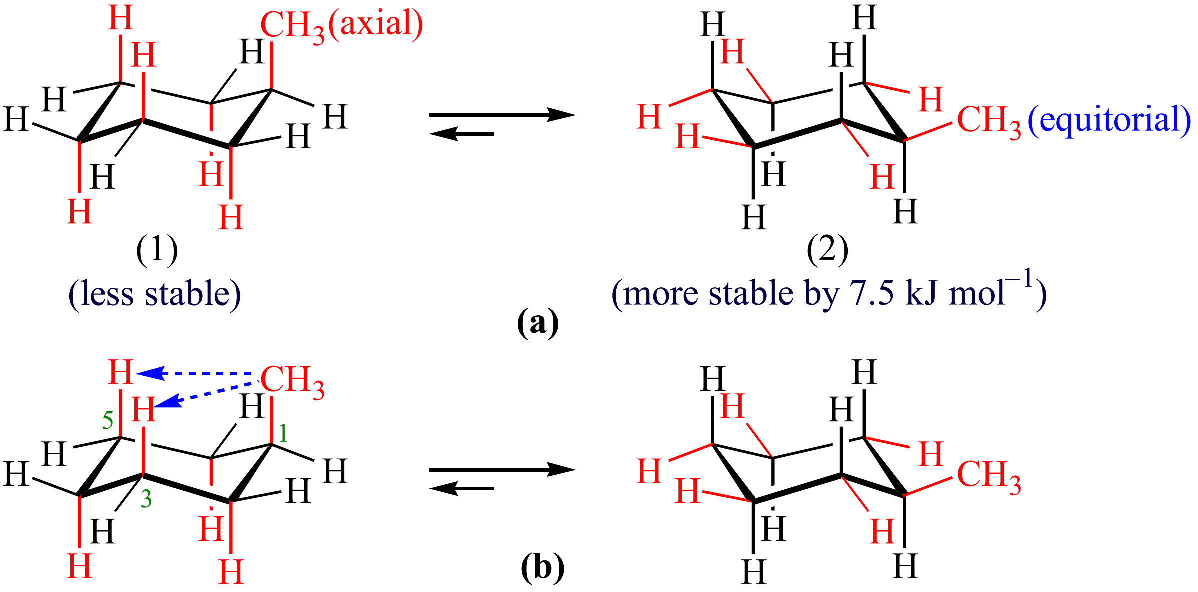


Figure 4.20 (a) The conformations of methylcyclohexane with the methyl group axial (1) and and equatorial (2). (b) 1,3-Diaxial interactions between the two axial hydrogen atoms and the axial methyl group in the axial conformation of methylcylohexane are shown with dashed arrows. Less crowding occurs in the equatorial conformation.

2) The conformation of methylcyclohexane with an **equatorial methyl** group is more stable than the conformation with an **axial methyl** group by 7.6 kJ mol^{-1}.

Table 4.7 **Relationship Between Free-energy Difference and Isomer Percentages for Isomers at Equilibrium at 25 °C**

Free-energy Difference $\Delta G°$ (kJ mol^{-1})		K	More Stable Isomer (%)	Less Stable Isomer (%)	M/L
0	(0)[b]	1.00	50	50	1.00
1.7	(0.41)[b]	1.99	67	33	2.03
2.7	(0.65)[b]	2.97	75	25	3.00
3.4	(0.81)[b]	3.95	80	20	4.00
4	(0.96)[b]	5.03	83	17	4.88
5.9	(1.41)[b]	10.83	91	9	10.11
7.5	(1.79)[b]	20.65	95	5	19.00
11	(2.63)[b]	84.86	99	1	99.00
13	(3.11)[b]	190.27	99.5	0.5	199.00
17	(4.06)[b]	956.56	99.9	0.1	999.00
23	(5.50)[b]	10782.67	99.99	0.01	9999.00

[a] $\Delta G° = -2.303\ RT \log K. \Rightarrow K = e^{-\Delta G°/RT}$ [b] In Kcal mol^{-1}.

Table 4-2 **The relationship between stability and isomer percentages at equilibrium**[a]

More stable isomer (%)	Less stable isomer (%)	Energy difference (25 °C) (*kcal/mol*)	(*kJ/mol*)
50	50	0	0
75	25	0.651	2.72
90	10	1.302	5.45
95	5	1.744	7.29
99	1	2.722	11.38
99.9	0.1	4.092	17.11

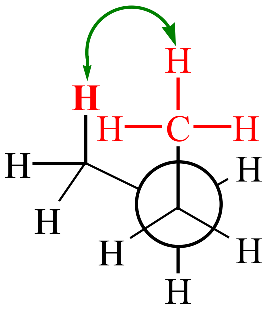
[a]The values in this table are calculated from the equation $K = e^{-\Delta E/RT}$, where K is the equilibrium constant between isomers; $e \approx 2.718$ (the base of natural logarithms); ΔE = energy difference between isomers; T = absolute temperature (in kelvins); and R = 1.986 cal/mol×K (the gas constant).

3) In the equilibrium mixture, the conformation of methylcyclohexane with an **equatorial methyl** group is the predominant one (~95%).

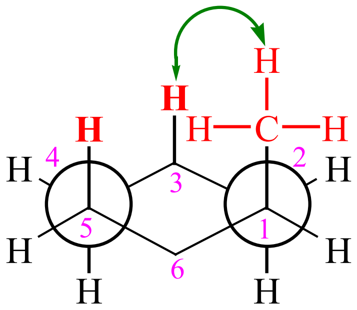
4) **1,3-Diaxial interaction:** the **axial methyl group** is so close to the two **axial**

hydrogen atoms on the same side of the molecule (attached to C3 and C5 atoms) that the van der Waals forces between them are **repulsive**.

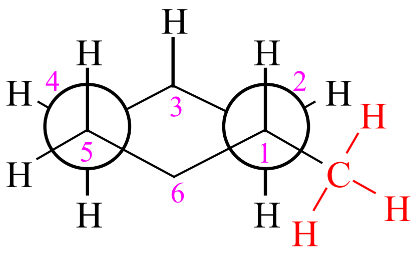
i) The strain caused by a **1,3-diaxial interaction** in methylcyclohexane is the same as the ***gauche interaction***.



***gauche*-Butane**
(3.8 kJ mol^{-1} steric strain)



Axial methylchclohexane
(two gauche interactions = 7.6 kJ mol^{-1} steric strain)



Equatorial methylchclohexane

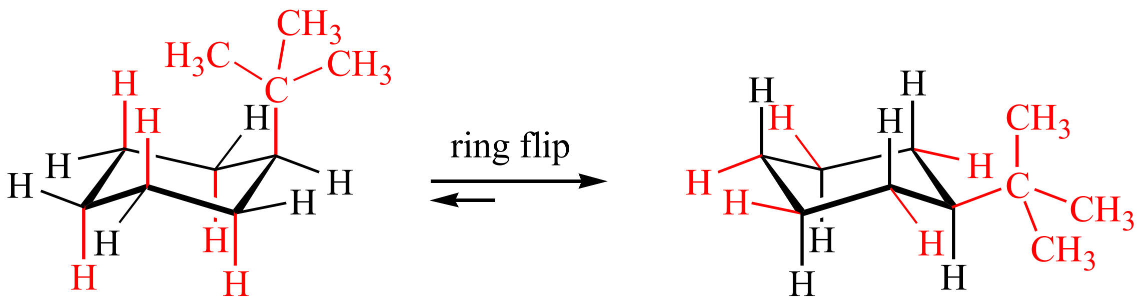
ii) The **axial methyl** group in methylcyclohexane has two ***gauche interaction***, and therefore it has of 7.6 kJ mol^{-1} steric strain.

iii) The **equatorial methyl** group in methylcyclohexane does not have a ***gauche interaction*** because it is ***anti*** to C3 and C5.

4. The conformation of *tert*-butylcyclohexane with *tert*-butyl group **equatorial** is **more than 21 kJ mol^{-1} more stable** than the **axial** form.

1) At room temperature, 99.99% of the molecules of *tert*-butylcyclohexane have the *tert*-butyl group in the **equatorial** position due to the large energy difference between the two conformations.

2) The molecule is **not conformationally** "**locked**". It still flips from one chair conformation to the other.

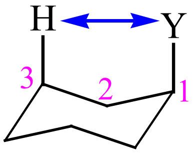


Equatorial *tert*-butylcyclohexane **Axial *tert*-butylcyclohexane**

Figure 4.21 Diaxial interactions with the large *tert*-butyl group axial cause the conformation with the *tert*-butyl group equatorial to be the predominant one to the extent of 99.99%.

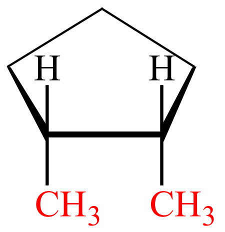
5. There is generally **less repulsive interaction** when the groups are **equatorial**.

Table 4-3 Steric strain due to 1,3-diaxial interactions

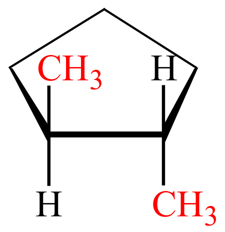
Y	*Strain of one* H–Y *1,3-diaxial interaction* (*kcal/mol*)	(*kJ/mol*)	
–F	0.12	0.5	
–Cl	0.25	1.4	
–Br	0.25	1.4	
–OH	0.5	2.1	
$–CH_3$	0.9	3.8	
$–CH_2CH_3$	0.95	4.0	
$–CH(CH_3)_2$	1.1	4.6	
$–C(CH_3)_3$	2.7	11.3	
$–C_6H_5$	1.5	6.3	
–COOH	0.7	2.9	
–CN	0.1	0.4	

4.14 DISUBSTITUTED CYCLOHEXANES: *CIS-TRANS* ISOMERISM

1. ***Cis-trans* isomerism:**

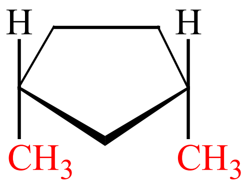


cis-1,2-Dimethylcyclopentane
bp 99.5 °C

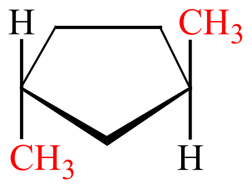


trans-1,2-Dimethylcyclopentane
bp 91.9 °C

Figure 4.22 _cis_- and _trans_-1,2-Dimethylcyclopentanes.



cis-1,3-Dimethylcyclopentane



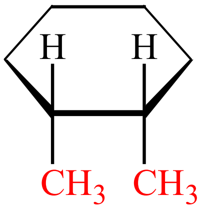
trans-1,3-Dimethylcyclopentane

1. The *cis*- and *trans*-1,2-dimethylcyclopentanes are **stereoisomers**; the *cis*- and *trans*-1,3-dimethylcyclopentanes are **stereoisomers**.
   1) The physical properties of *cis*-*trans* isomers are different: they have different **melting points**, **boiling points**, and so on.

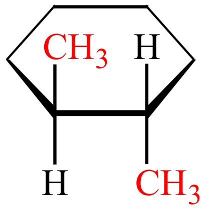
Table 4.8 The Physical Constants of _Cis_- and _Taans_-Disubstituted Cyclohexane Derivatives

Substituents	Isomer	mp (°C)	bp (°C)[a]
1,2-Dimethyl-	*cis*	–50.1	130.04^{760}
1,2-Dimethyl-	*trans*	–89.4	123.7^{760}
1,3-Dimethyl-	*cis*	–75.6	120.1^{760}
1,3-Dimethyl-	*trans*	–90.1	123.5^{760}
1,2-Dichloro-	*cis*	–6	93.5^{22}
1,2-Dichloro-	*trans*	–7	74.7^{16}

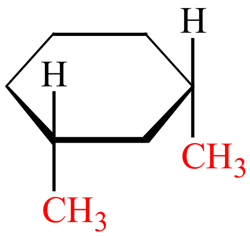
[a]The pressures (in units of torr) at which the boiling points were measured are given as superscripts.



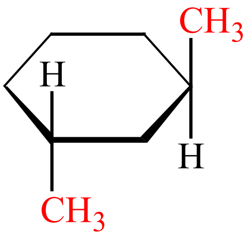
***cis*-1,2-Dimethylcyclohexane**



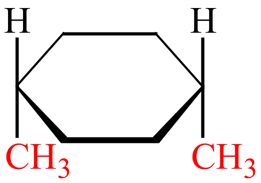
***trans*-1,2-Dimethylcyclohexane**



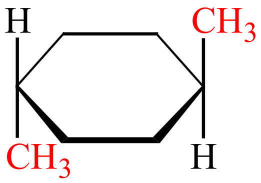
***cis*-1,3-Dimethylcyclohexane**



***trans*-1,3-Dimethylcyclohexane**



***cis*-1,4-Dimethylcyclohexane**



***trans*-1,4-Dimethylcyclohexane**

4.14A CIS-TRANS ISOMERISM AND CONFORMATIONAL STRUCTURES

1. There are two possible chair conformations of *trans*-1,4-dimethylcyclohexane:

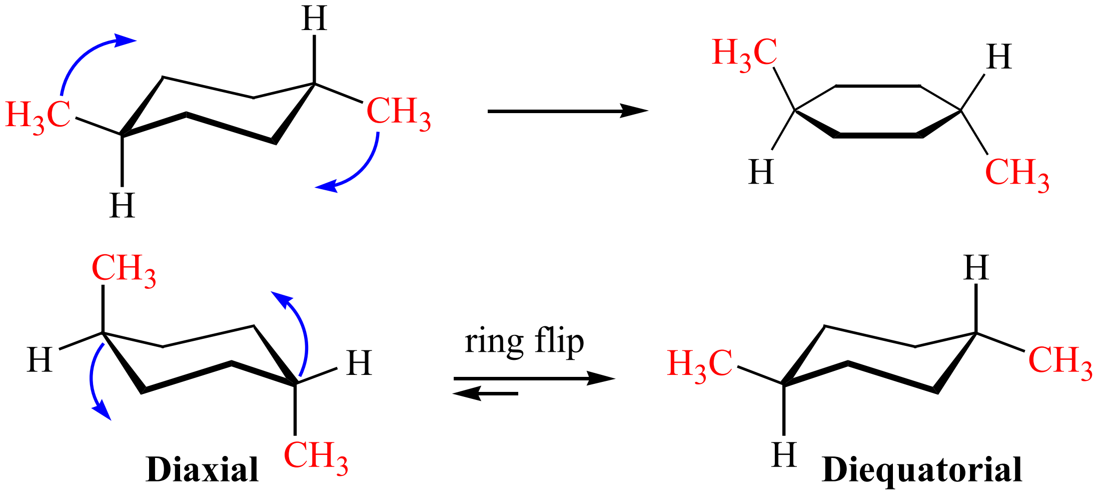
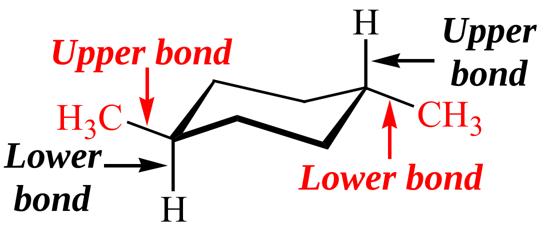


Figure 4.23 The two chair conformations of *trans*-1,4-dimethylcyclohexane. (Note: All other C–H bonds have been omitted for clarity.)

1) **Diaxial** and **diequatorial** *trans*-1,4-dimethylcyclohexane.

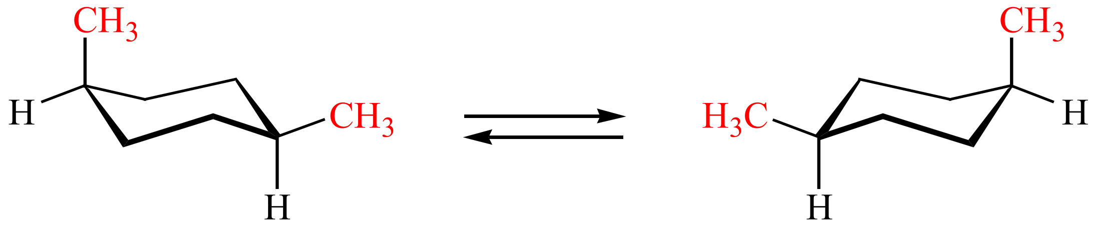
2) The **diequatorial** conformation is the **more stable** conformer and it represents at least 99% of the molecules at equilibrium.

2. In a ***trans*-disubstituted** cyclohexane, one group is attached by an ***upper*** bond and one by the ***lower*** bond; in a ***cis*-disubstituted** cyclohexane, both groups are attached by an ***upper*** bond or both by the ***lower*** bond.



***trans*-1,4-Dimethylcyclohexane** ***cis*-1,4-Dimethylcyclohexane**

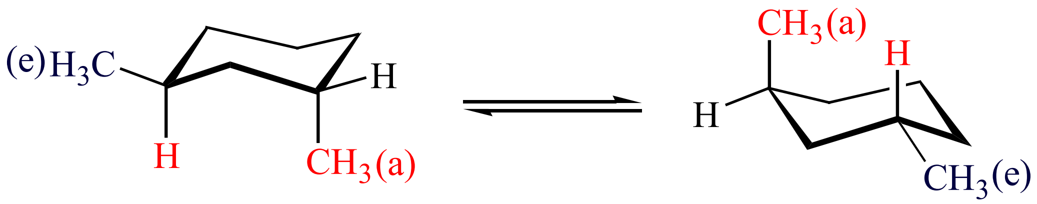
3. *cis*-1,4-Dimethylcyclohexane exists in two **equivalent** chair conformations:



Axial-equatorial **Equatorial-axial**

Figure 4.24 Equivalent conformations of *cis*-1,4-dimethylcyclohexane.

4. *trans*-1,3-Dimethylcyclohexane exists in two **equivalent** chair conformations:



***trans*-1,3-Dimethylcyclohexane**

5. *trans*-1,3-Disubstituted cyclohexane with two **different alkyl groups**, the conformation of **lower energy** is the one having the **larger group** in the **equatorial** position.

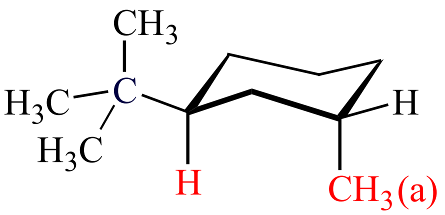
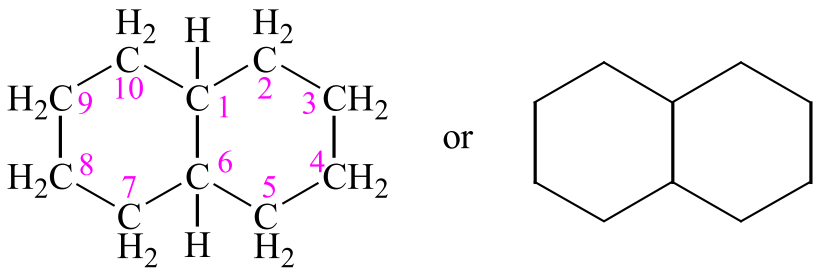


Table 4.9 Conformations of Dimethylcyclohexanes

Compound	*Cis* Isomer	*Trans* Isomer
1,2-Dimethyl	*a*,*e* or *e*,*a*	***e*,*e*** or *a*,*a*
1,3-Dimethyl	***e*,*e*** or *a*,*a*	*a*,*e* or *e*,*a*
1,4-Dimethyl	*a*,*e* or *e*,*a*	***e*,*e*** or *a*,*a*

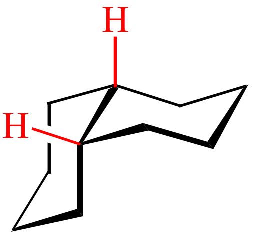
4.15 BICYCLIC AND POLYCYCLIC ALKANES

1. **Decalin (bicyclo[4.4.0]decane):**

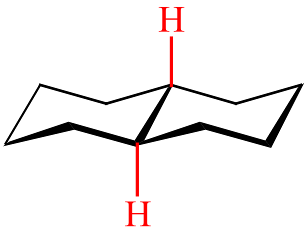


Decalin (bicyclo[4.4.0]decane)
(carbon atoms 1 and 6 are bridgehead carbon atoms)

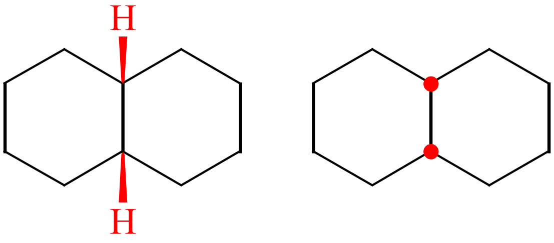
1) Decalin shows *cis*-*trans* isomerism:



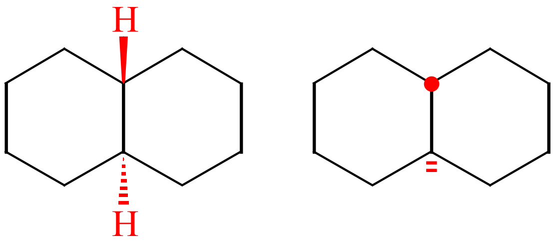
***cis*-Decalin**



***trans*-Decalin**



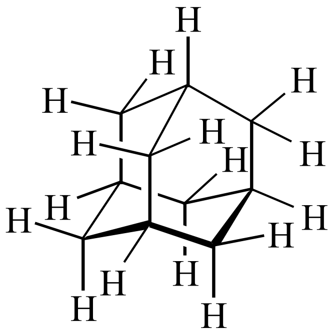
***cis*-Decalin**



***trans*-Decalin**

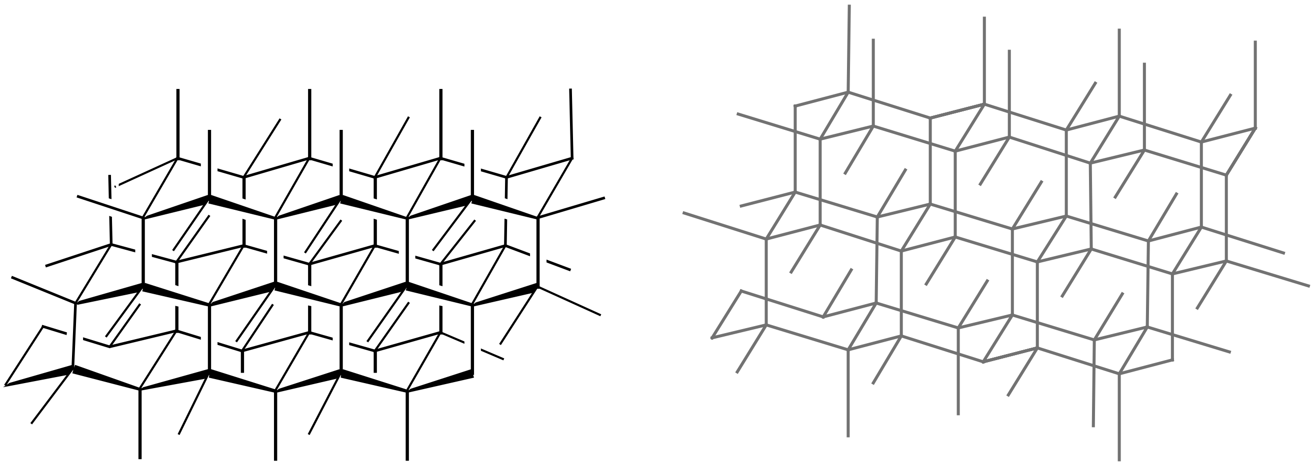
2) *cis*-Decalin boils at 195°C (at 760 torr) and *trans*-decalin boils at 185.5°C (at 760 torr).

2. **Adamantane:** a tricyclic system contains cyclohexane rings, all of which are in the chair form.



Adamantane

3. **Diamond:**



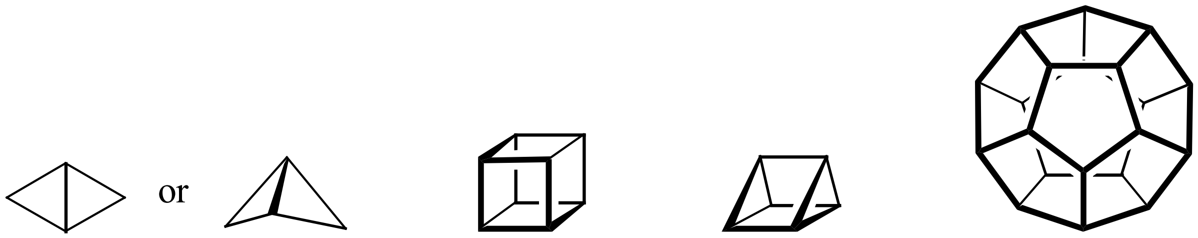
1) The great hardness of diamond results from the fact that the entire diamond crystal is actually one very large molecule.

2) There are other ***allotropic forms*** of carbon, including graphite, Wurzite carbon

[with a structure related to Wurzite (ZnS)], and a new group of compounds called **fullerenes**.

4. **Unusual** (sometimes highly strained) **cyclic hydrocarbon:**

1) In 1982, Leo A. Paquette's group (Ohio State University) announced the successful synthesis of the "**complex, symmetric, and aesthetically appealing**" molecule called **dodecahedrane**. (aesthetic = esthetic, 美的, 審美上的; 風雅的)



Bicyclo[1,1,0]butane **Cubane** **Prismane** **Dodecahedrane**

4.16 PHEROMONES: COMMUNICATION BY MEANS OF CHEMICALS

1. Many animals, ***especially insects***, communicate with other members of their species based on the **odors** of **pheromones**.

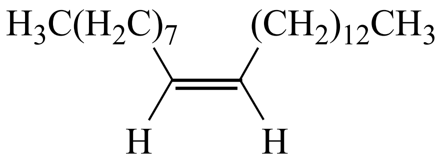
1) Pheromones are secreted by insects in extremely small amounts but they can cause profound and varied biological effects.

2) Pheromones are used as **sex attractants** in courtship, **warning substances**, or "**aggregation compounds**" (to cause members of their species to congregate).

3) Pheromones are often relatively simple compounds.

$CH_3(CH_2)_9CH_3$	$(CH_3)_2CH(CH_2)_{14}CH_3$
Undecane	**2-Methylheptadecane**
(cockroach aggregation pheromone)	**(sex attractant of female tiger moth)**

4) **Muscalure** is the sex attractant of the common housefly (*Musca domestica*).



Muscalure (sex attractant of common housefly)

4) Many insect sex attractants have been synthesized and are used to **lure** insects into traps as a means of insect control.

4.17 Chemical Reactions of Alkanes

1. **C—C** and **C—H** bonds are quite strong: alkanes are generally inert to many chemical reagents.
   1) **C—H** bonds of alkanes are only **slightly polarized** ⇒ alkanes are generally unaffected by most bases.
   2) Alkane molecules have **no unshared electrons** to offer sites for attack by acids.
   3) *Paraffins* (Latin: *parum affinis*, little affinity).
2. Reactivity of alkanes:
   1) Alkanes react vigorously with oxygen when an appropriate mixture is ignited —— **combustion**.
   2) Alkanes react with **chlorine** and **brmine** when **heated**, and they react explosively with **fluorine**.

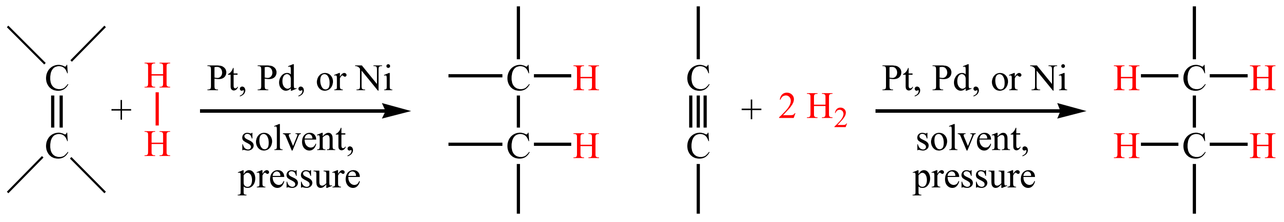
4.18 Synthesis of Alkanes and Cycloalkanes

4.18A Hydrogenation of Alkenes and Alkynes

1. **Catalytic hydrogenation:**
   1) Alkenes and alkynes react with hydrogen in the presence of metal catalysts such

as nickel, palladium, and platinum to produce alkanes.

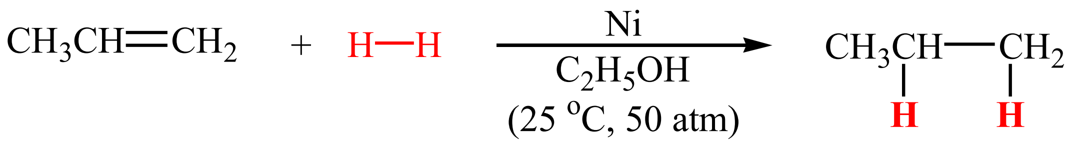
General Reaction



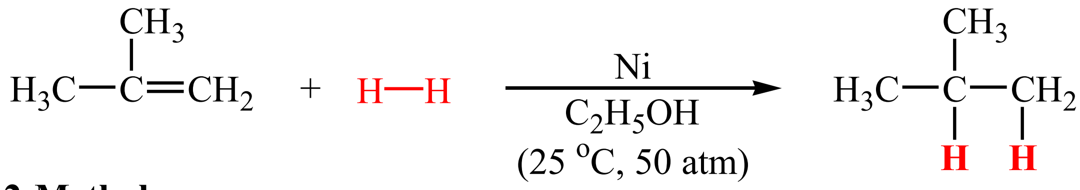
Alkene **Alkane** **Alkyne** **Alkane**

2) The reaction is usually carried out by dissolving the alkene or alkyne in a solvent such as ethyl alcohol (C_2H_5OH), adding the metal catalyst, and then exposing the mixture to hydrogen gas under pressure in a special apparatus.

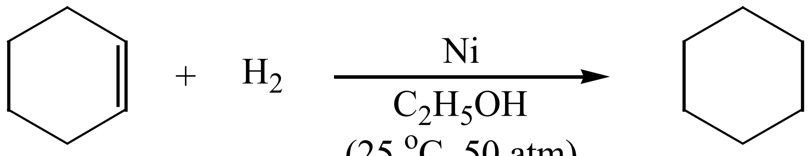
Specific Examples



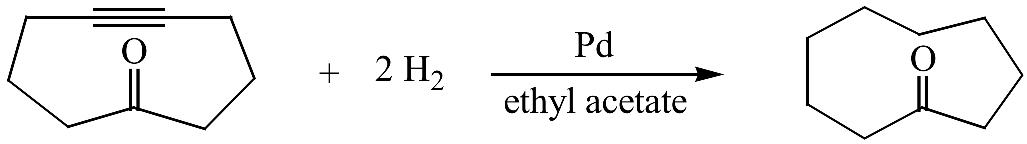
propene **propane**



2-Methylpropene **Isobutane**



Cyclohexene **Cyclohexane**



5-Cyclononynone **Cyclononanone**

4.18B REDUCTION OF ALKYL HALIDES

1. Most alkyl halides react with zinc and aqueous acid to produce an alkane.

General Reaction

$$R{-}X + Zn + HX \longrightarrow R{-}H + ZnX_2$$

or*

$$R{-}X \xrightarrow[(-ZnX_2)]{Zn,\ HX} R{-}H$$

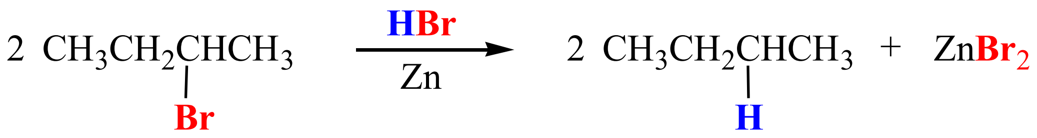
1) *Abbreviated equations for organic chemical reactions:

i) The organic reactant is shown on the left and the organic product on the right.

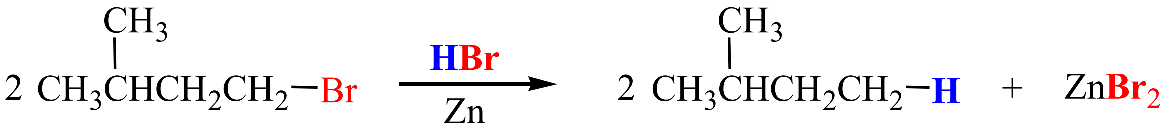
ii) The reagents necessary to bring about the transformation are written over (or under) the arrow.

iii) The equations are often left unbalanced, and sometimes by-products (in this case, ZnX_2) are either omitted or are placed under the arrow in parentheses with a minus sign, for example, ($-ZnX_2$).

Specific Examples



***sec*-Butyl bromide (2-bromobutane)** → **Butane**

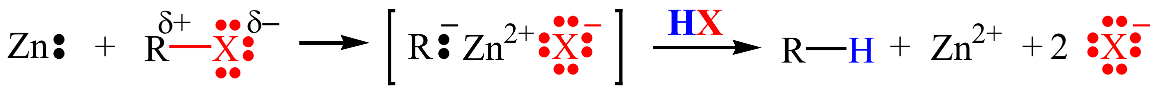


Isopentyl bromide (1-bromo-3-methylbutane) → **Isopentane (2-methylbutane)**

2. The reaction is a **reduction** of alkyl halide: zinc atoms transfer electrons to the carbon atom of the alkyl halide.

1) Zinc is a good reducing agent.

2) The possible mechanism for the reaction is that an alkylzinc halide forms first and then reacts with the acid to produce the alkane:



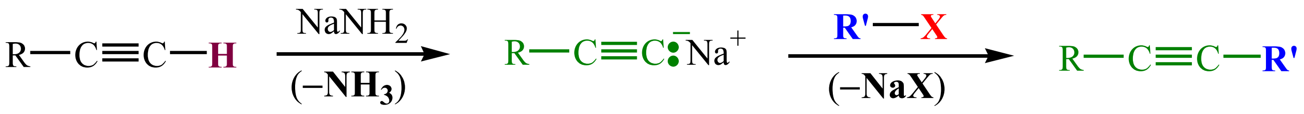
Reducing agent **Alkylzinc halide** **Alkane**

4.18C ALKYLATION OF TERMINAL ALKYNES

1. **Terminal alkyne:** an alkyne with a hydrogen attached to a triply bonded carbon.
   1) The **acetylenic hydrogen** is weakly acidic (pK_a ~ 25) and can be removed with a strong base (e.g. $NaNH_2$) to give an anion (called an alkynide anion or **acetylide ion**).

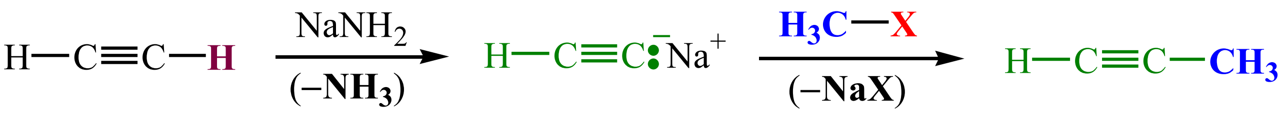
2. **Alkylation:** the **formation of a new C—C bond** by replacing a **leaving group** on an **electrophile** with a **nucleophile**.

General Reaction



An alkyne **Sodium amide** **An alkynide anion** **R' must be methyl or 1° and unbranched at the second carbon**

Specific Examples

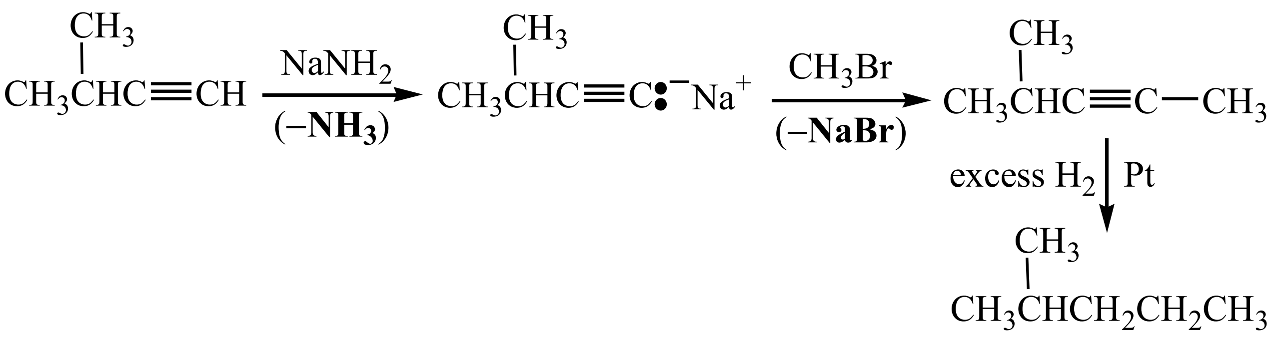


Ethyne (acetylene) **Ethynide anion (acetylide anion)** **Propyne 84%**

3. **The alkyl halide used with the alkynide anion must be methyl or primary and also unbranched at its second (beta) carbon**.
   1) Alkyl halides that are 2° or 3°, or are 1° with branching at the beta carbon, undergo **elimination** reaction predominantly.

4. After alkylation, the **alkyne triple bond** can be used in other reactions:
   1) It would not work to use propyne and 2-bromopropane for the alkylation step of

this synthesis.



4.19 SOME GENERAL PRINCIPLES OF STRUCTURE AND REACTIVITY: A LOOK TOWARD SYNTHESIS

1. **Structure and reactivity:**

1) Preparation of the alkynide anion involves simple Brønsted-Lowry acid-base chemistry.

i) The acetylenic hydrogen is weakly acidic (pK_a ~ 25) and can be removed with a strong base.

2) The alkynide anion is a Lewis base and reacts with the alkyl halide (as an electron pair acceptor, a Lewis acid).

i) The alkynide anion is a ***nucleophile*** which is a reagent that seeks **positive charge**.

ii) The alkyl halide is a ***electrophile*** which is a reagent that seeks **negative charge**.

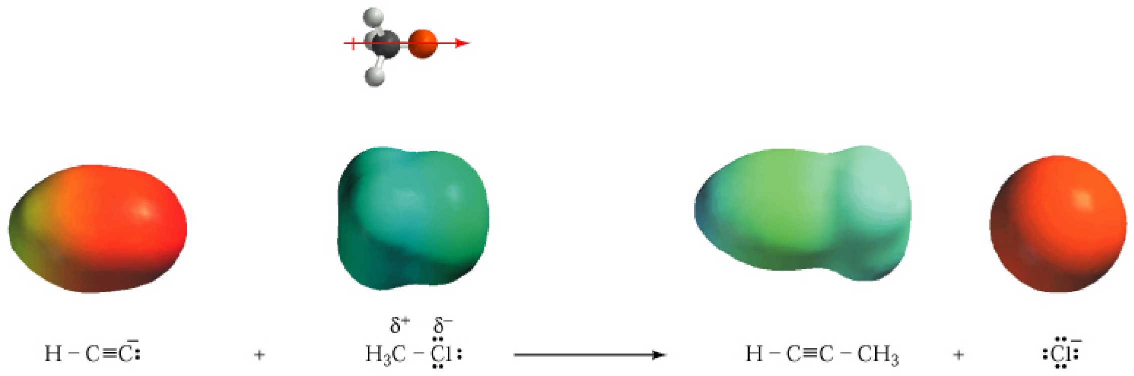


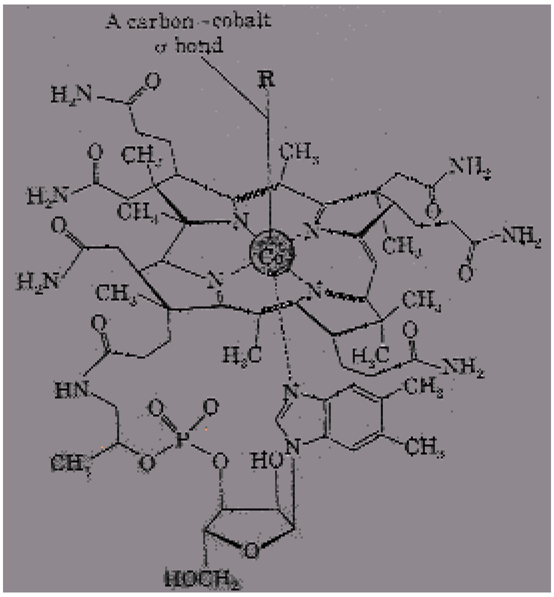
Figure 4.25 The reaction of ethynide (acetylide) anion and chloromethane.

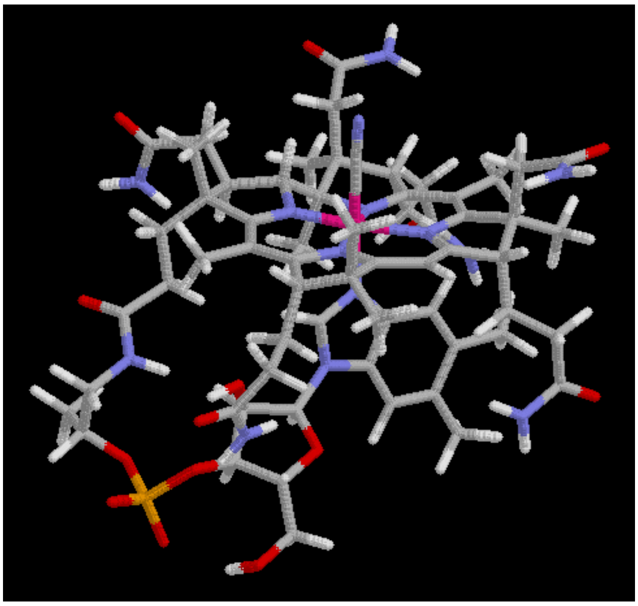
Electrostatic potential maps illustrate the complementary nucleophilic and electrophilic character of the alkynide anion and the alkyl halide.

2. The reaction of acetylide anion and chloromethane:
   1) The acetylide anion has strong localization of negative charge at its terminal carbon (indicated by red in the electrostatic potential map).
   2) Chloromethane has partial positive charge at the carbon bonded to the electronegative chlorine atom.
   3) The acetylide anion acting as a Lewis base is attracted to the partially positive carbon of the 1° alkyl halide.
   4) Assuming a collision between the two **occurs with the proper orientation and sufficient kinetic energy**, as the acetylide anion brings two electrons to the alkyl halide to form a new bond and it will displace the halogen from the alkyl halide.
   5) The halogen leaves as an anion with the pair of electrons that formerly bonded it to the carbon.

4.20 AN INTRODUCTION TO ORGANIC SYNTHESIS

1. Organic synthesis is the process of building organic molecules from simpler precursors.
2. Purposes for organic synthesis:
   1) For developing new drugs ⇒ to discover molecules with structural attributes that enhance certain medical effects or reduce undesired side effects ⇒ e.g. Crixivan (an HIV protease inhibito, Chapter 2).
   2) For mechanistic studies ⇒ to test some hypothesis about a reaction mechanism or about how a certain organism metabolizes a compound ⇒ often need to synthesize a particularly "labeled" compound (with deuterium, tritium, or ^{13}C).
3. The total synthesis of vitamin B_{12} is a monumental synthetic work published by R. B. Woodward (Harvard) and A. Eschenmoser (Swiss Federal Institute of Technology):





1) The synthesis of vitamin B_{12} took 11 years, required 90 steps, and involved the work of nearly 100 people.

4. Two types of transformations involved in organic synthesis:
   1) Converting functional groups from one to another.
   2) Creating new C—C bonds.

5. **The heart of organic synthesis is the orchestration of functional group interconversions and C—C bond forming steps.**

4.20A Retrosynthetic Analysis —— Planning an Organic Syntheses

1. **Retrosynthetic Analysis:**
   1) Often, the sequence of transformations that would lead to the desired compound (**target**) is too complex for us to "**see**" a path from the beginning to the end.
      i) We envision the sequence of steps that is required in a backward fashion, one step at a time.

   2) Begin by identifying immediate precursors that could be transformed to the target molecule.
   3) Then, identifying the next set of precursors that could be used to make the

intermediate target molecules.

4) Repeat the process until compounds that are sufficiently simple that they are readily available in a typical laboratory.

Target molecule ⇒ **1st precursor** ⇒ **2nd precursor** ⇒ ⇒ **Starting compound**

5) The process is called **retrosynthetic analysis**.

i) ⇒ is a **retrosynthetic arrow** (**retro** = **backward**) that relates the target molecule to its most immediate precursors. Professor E. J. Corey originated the term **retrosynthetic analysis** and was the first to state its principles formerly.

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E. J. Corey (Harvard University, 1990 Chemistry Nobel Prize winner)

2. Generate as many possible precursors when doing retrosynthetic analysis, and hence different synthetic routes.

Target molecule ⇒ **1st precursor A** ⇒ **2st precursors a**, **2st precursors b**

Target molecule ⇒ **1st precursor B** ⇒ **2st precursors c**, **2st precursors d**

Target molecule ⇒ **1st precursor C** ⇒ **2st precursors e**, **2st precursors f**

Figure 4.26 Retrosynthetic analysis often disclose several routes form the target molecule back to varied precursors.

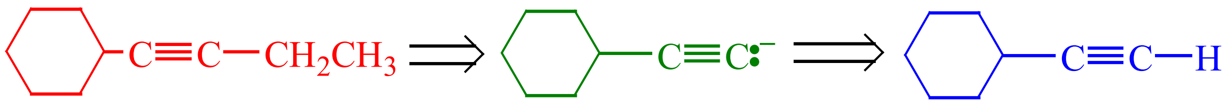
1) **Evaluate** all the **possible advantages** and **disadvantages** of each path ⇒ determine the most efficient route for synthesis.

2) **Evaluation** is based on **specific restrictions** and **limitations** of reactions in the sequence, the **availability of materials**, and other factors.

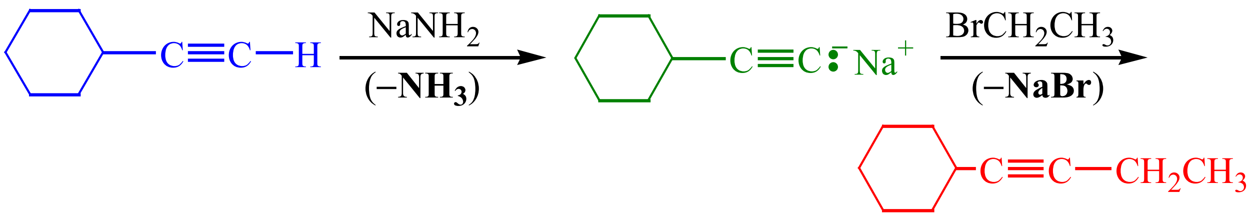
3) In reality, it may be necessary to try several approaches in the laboratory in order to find the most efficient or successful route.

4.20B Identifying Precursors

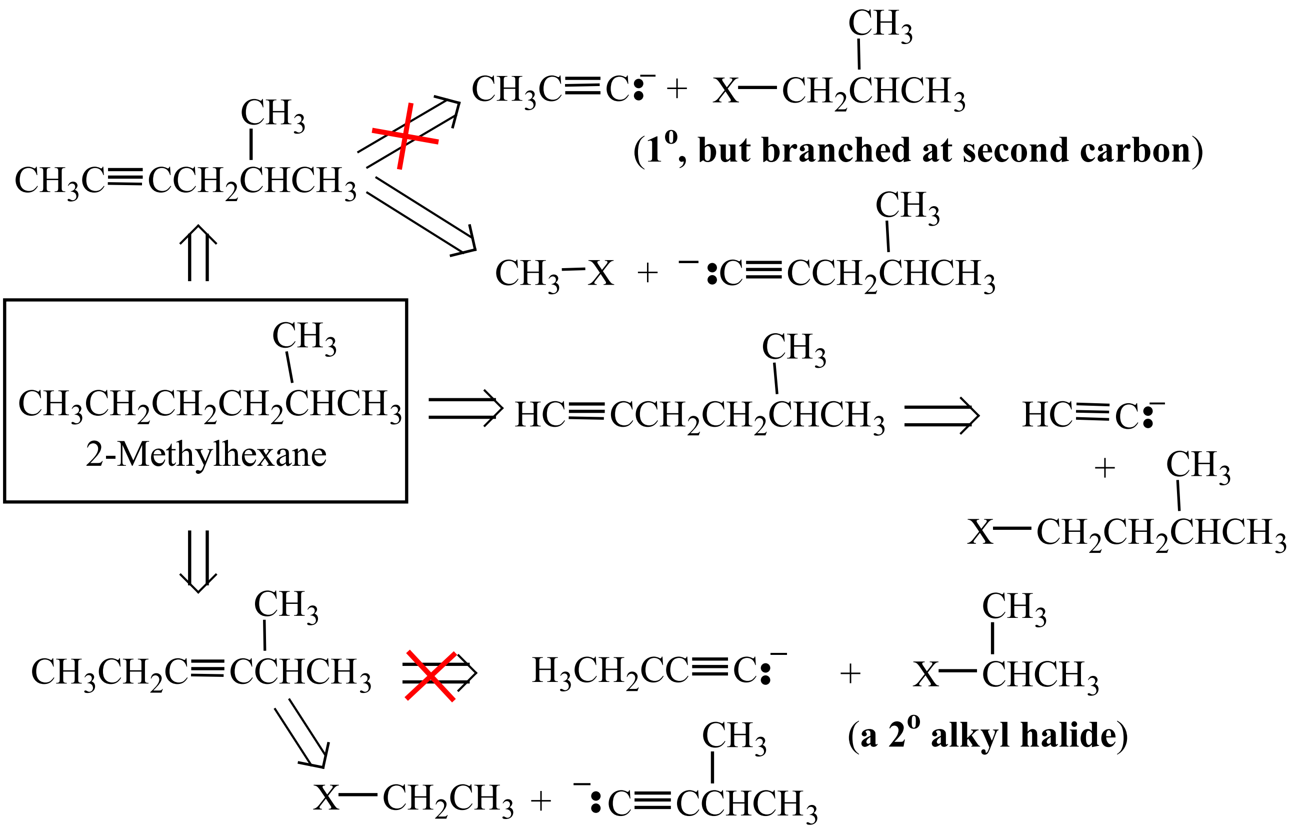
Retrosynthetic Analysis



Synthesis



Retrosynthetic Analysis



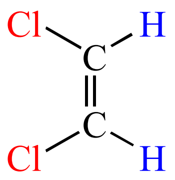
STEREOCHEMISTRY: CHIRAL MOLECULES

5.1 ISOMERISM: CONSTITUTIONAL ISOMERS AND STEREOISOMERS

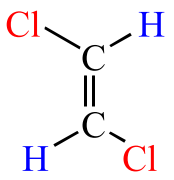
1. **Isomers** are different compounds that have the same molecular formula.
2. **Constitutional isomers** are isomers that differ because their atoms are connected in a different order.

Molecular Formula	Constitutional isomers		
C_4H_{10}	$CH_3CH_2CH_2CH_3$ **Butane**	and	CH_3 | $H_3C-CH-CH_3$ **Isobutane**
C_3H_7Cl	$CH_3CH_2CH_2Cl$ **1-Chloropropane**	and	Cl | $H_3C-CH-CH_3$ **2-Chloropropane**
C_2H_6O	CH_3CH_2OH **Ethanol**	and	CH_3OCH_3 **Dimethyl ether**

3. **Stereoisomers** differ only in arrangement of their atoms in space.

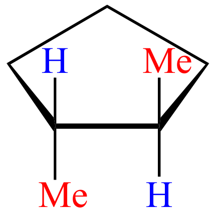


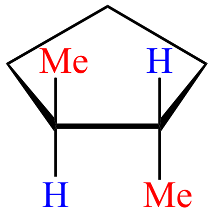
cis-1,2-Dichloroethene ($C_2H_2Cl_2$)



trans-1,2-Dichloroethene ($C_2H_2Cl_2$)

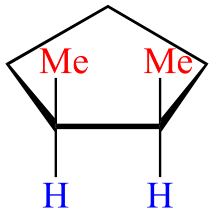
4. **Ennatiomers** are stereoisomers whose molecules are ***nonsuperposable mirror images of each other***.



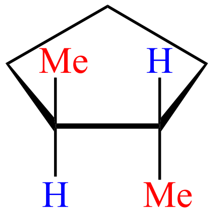


trans-1,2-Dimethylcyclopentane (C_7H_{14})   *trans*-1,2-Dimethylcyclopentane (C_7H_{14})

5. **Diastereomers** are stereoisomers whose molecules are *not* ***mirror images of each other***.



cis-1,2-Dimethylcyclopentane
(C_7H_{14})



trans-1,2-Dimethylcyclopentane
(C_7H_{14})

SUBDIVISION OF ISOMERS

Isomers

(Different compounds with same molecular formula)

Constitutional isomers

(Isomers whose atoms have a different connectivity)

Stereoisomers

(Isomers that have the same connectivity but differ in the arrangement of their atoms in space)

Enantiomers

(Stereoisomers that are nonsuperposable mirror images of each other)

Diastereomers

(Stereoisomers that are not mirror images of each other)

5.2 ENANTIOMERS AND CHIRAL MOLECULES

1. A **chiral** molecule is one that is *not* ***identical with its mirror image***.

2. Objects (and molecules) that *are* superposable on their mirror images are ***achiral***.

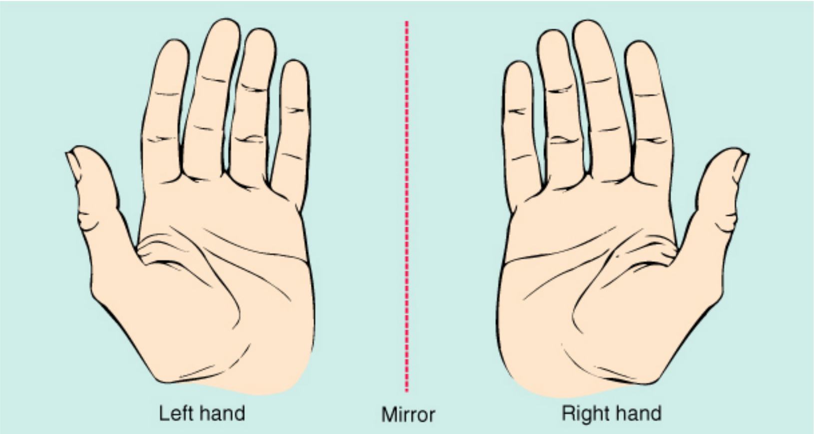


Figure 5.1 The mirror image of a left hand is aright hand.

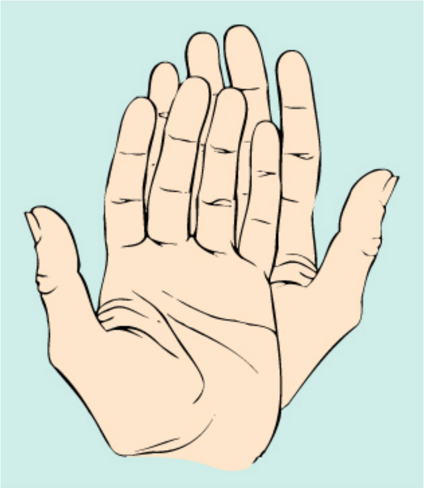


Figure 5.2 Left and right hands are not superposable.

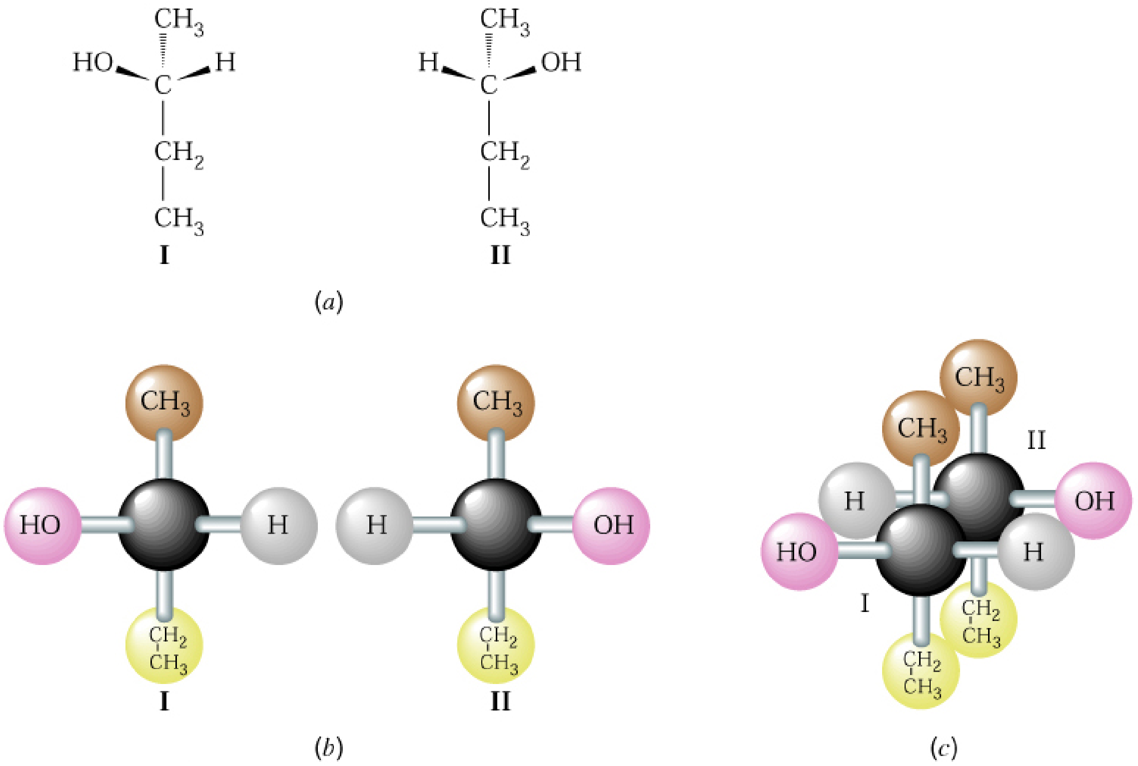


Figure 5.3 (a) Three-dimensional drawings of the 2-butanol enantiomers I and II. (b) Models of the 2-butanol enantiomers. (c) An unsuccessful attempt to superpose models of I and II.

3. A ***stereocenter*** is defined as ***an atom bearing groups of such nature that an interchange of any two groups will produce a stereoisomer***.

A tetrahedral atom with four different groups attached to it is a ***stereocenter*** (***chiral center***, ***stereogenic center***)

A tetrahedral carbon atom with four different groups attached to it is an ***asymmetric carbon***.

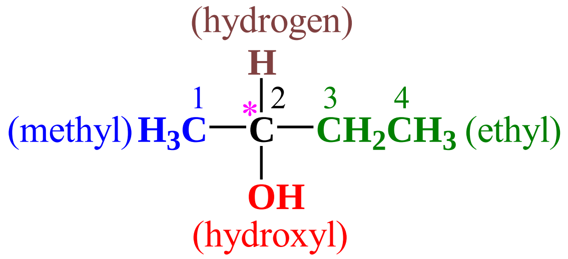


Figure 5.4 The tetrahedral carbon atom of 2-butanol that bears four different groups. [By convention such atoms are often designated with an asterisk (*)].

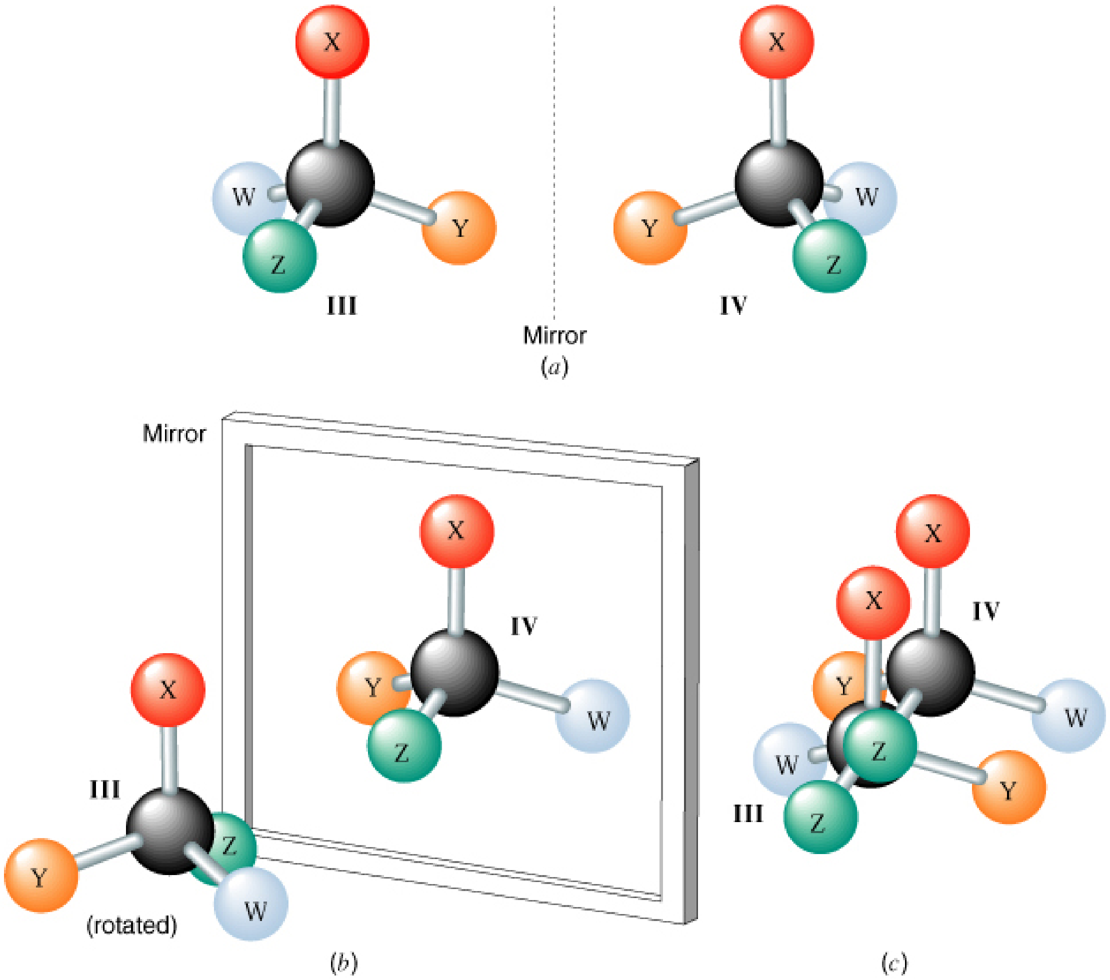


Figure 5.5 A demonstration of chirality of a generalized molecule containing one tetrahedral stereocenter. (a) The four different groups around the carbon atom in III and IV are arbitrary. (b) III is rotated and placed in front of a mirror. III and IV are found to be related as an object and its mirror image. (c) III and IV are not superposable; therefore, the molecules that they represent are chiral and are enantiomers.

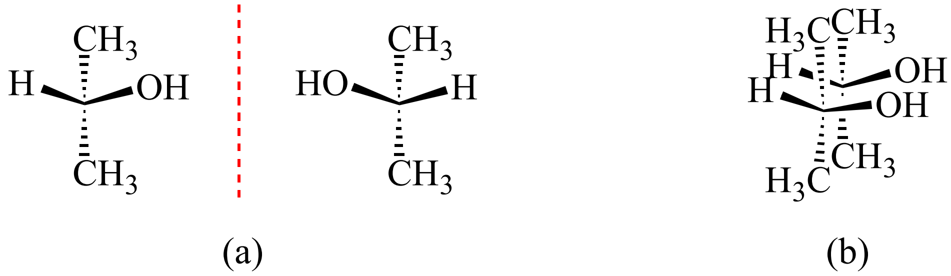
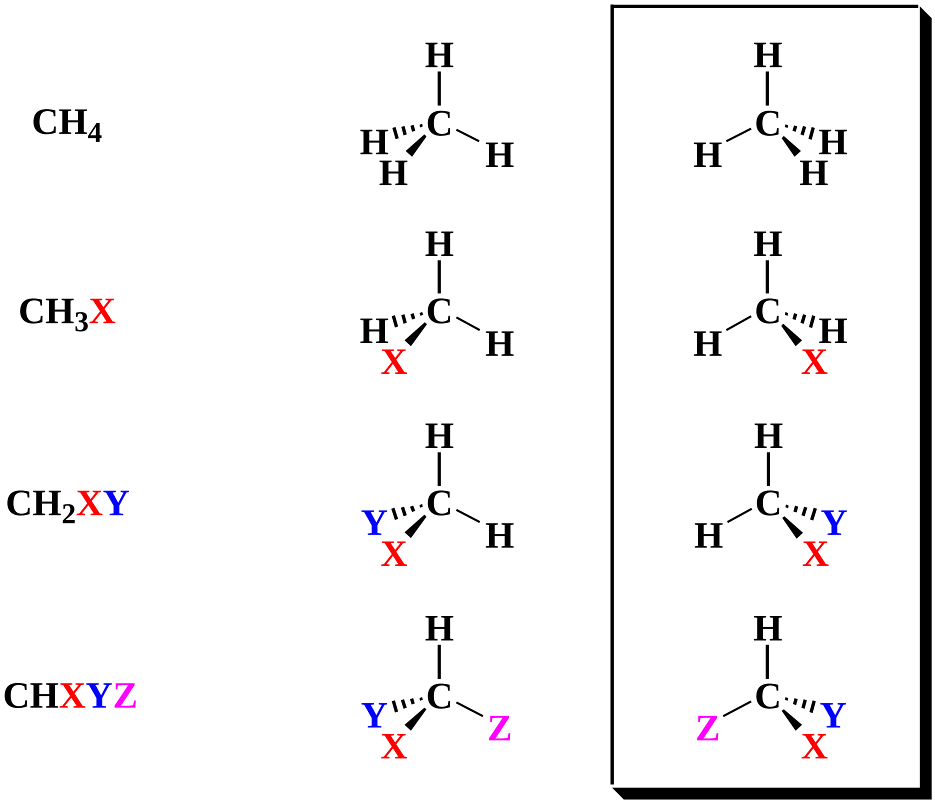
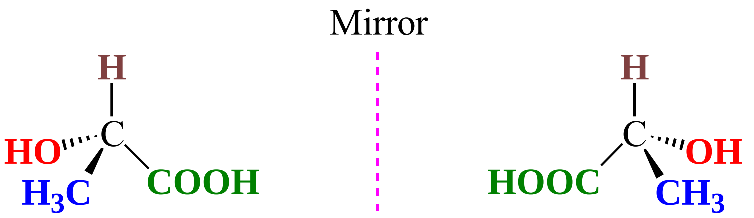
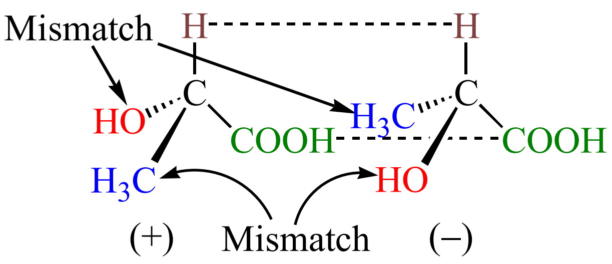


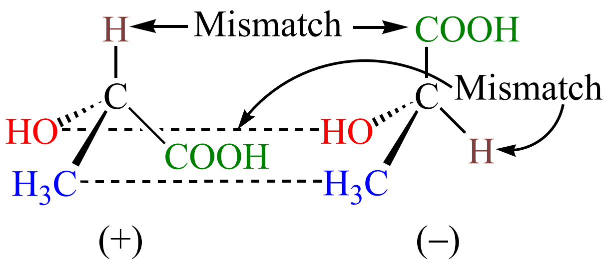
Figure 5.6 **(a) 2-Propanol (V) and its mirror image (VI), (b) When either one is rotated, the two structures are superposable and so do not represent enantiomers. They represent two molecules of the same compound. 2-Propanol does not have a stereocenter.**

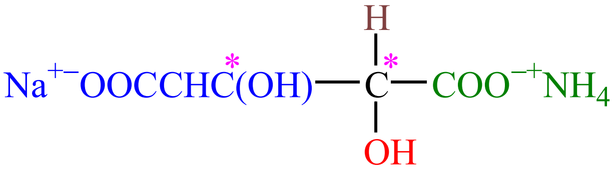




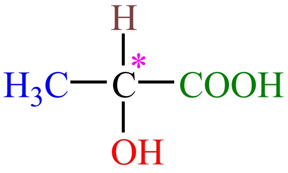
(+)-Lactic acid, $[\alpha]_D = +3.82$ (−)-Lactic acid, $[\alpha]_D = -3.82$



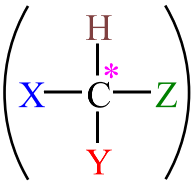




Sodium ammonium tartrate



Lactic acid

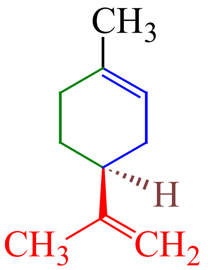


5.3 THE BIOLOGICAL IMPORTANCE OF CHIRALITY

1. Chirality is a phenomenon that pervades the university.
   1) The human body is structurally chiral.
   2) Helical seashells are chiral, and most spiral like a right-handed screw.
   3) Many plants show chirality in the way they wind around supporting structures.
      i) The honeysuckle (忍冬;金銀花), *Lonicera sempervirens*, winds as a left-handed helix.
      ii) The bindweed (旋花類的植物), *Convolvuus sepium*, winds as a right-handed way.
2. Most of the molecules that make up plants and animals are chiral, and usually only one form of the chiral molecule occurs in a given species.
   1) All but one of the 20 amino acids that make up naturally occurring proteins are chiral, and all of them are classified as being left handed (*S* configuration).
   2) The molecules of natural sugars are almost all classified as being right handed (*R* configuration), including the sugar that occurs in DNA.
   3) DNA has a helical structure, and all naturally occurring DNA turns to the right.

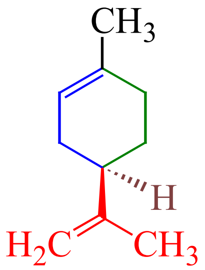
CHIRALITY AND BIOLOGICAL ACTIVITY

S



lemon odor

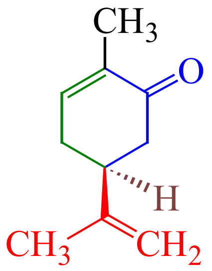
Limonene



orange odor

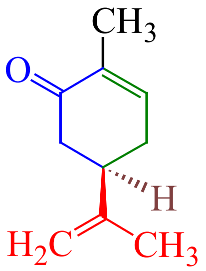
R

S



spearmint fragrance

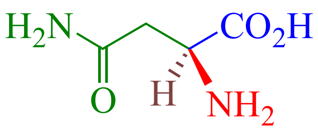
Carvone



caraway seed odor

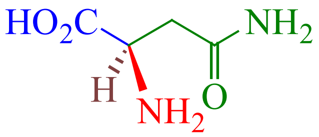
R

S



bitter taste

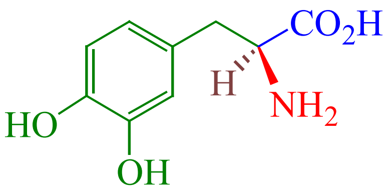
Asparagine



sweet taste

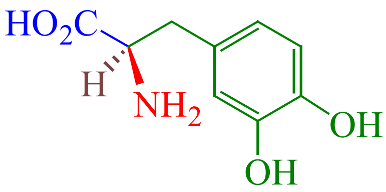
R

S



Anti-Parkinson's disease

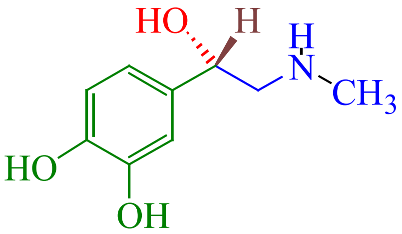
Dopa
(3,4-dihydroxyphenylalanine)



Toxic

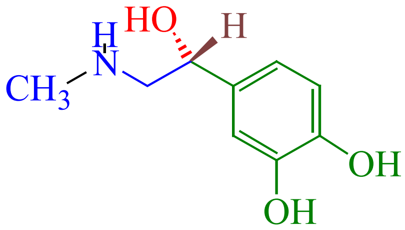
R

S



Toxic

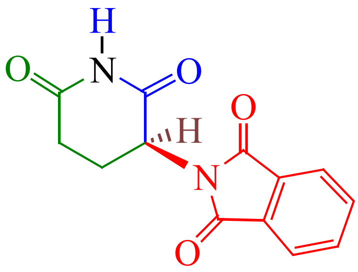
Epinephrine



hormone

R

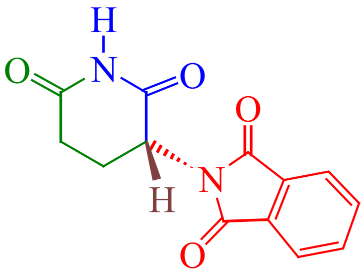
S



teratogenic activity

Thalidomide

sedative, hypnotic



causes **NO** deformities

R

3. Chirality and biological activity:

1) Limonene: *S*-limonene is responsible for the odor of lemon, and the *R*-limonene for the odor of orange.

2) Carvone: *S*-carvone is responsible for the odor of spearmint (荷蘭薄荷), and the *R*-carvone for the odor of caraway (香菜) seed.

3) Thalidomide: used to alleviate the symptoms of morning sickness in pregnant women before 1963.

   i) The *S*-enantiomer causes birth defect.

   ii) Under physiological conditions, the two enantiomers are interconverted.

   iii) Thalidomide is approved under highly strict regulations for treatment of a serious complication associated with leprosy (麻瘋病).

   iv) Thalidomide's potential for use against other conditions including AIDS, brain cancer, rheumatoid (風濕癥的) arthritis is under investigation.

4. The origin of biological properties relating to chirality:

1) The fact that **the enantiomers of a compound do not smell the same** suggests that **the receptor sites in the nose for these compounds are chiral**, and only the correct enantiomer will fit its particular site (just as a hand requires a glove of the ocrrect chirality for a proper fit).

2) The binding specificity for a chiral molecule (like a hand) at a chiral receptor site is only favorable in one way.

   i) If either the molecule or the biological receptor site had the wrong handedness, the natural physiological response (e.g. neural impulse, reaction catalyst) will not occur.

3) Because of the tetrahedral stereocenter of the amino acid, three-point binding can occur with proper alignment for only one of the two enantiomers.

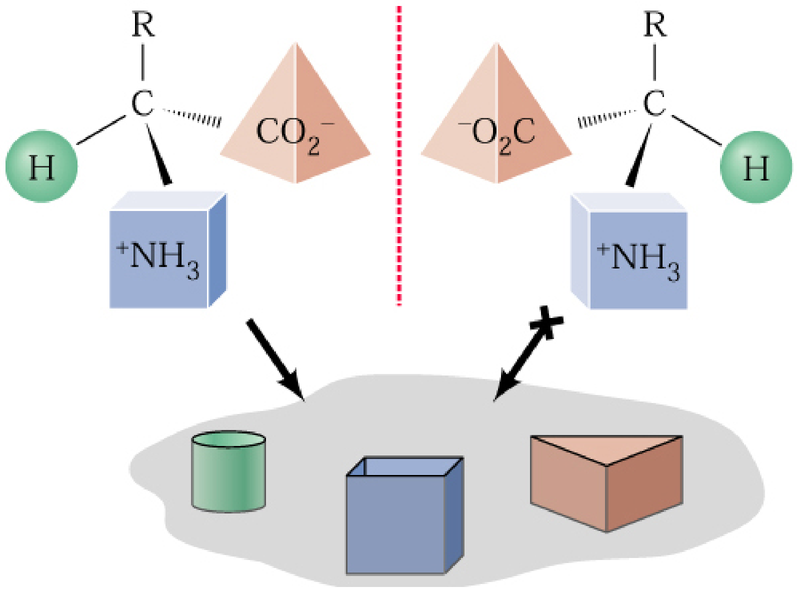


Figure 5.7 Only one of the two amino acid enantiomers shown can achieve three-point binding with the hypothetical binding site (e.g., in an enzyme).

5.4 HISTORICAL ORIGIN OF STEREOCHEMISTRY

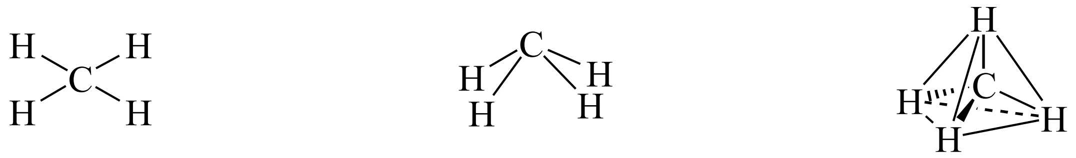
1. ***Stereochemistry***: founded by Louis Pasteur in 1848.
2. H. van't Hoff (Dutch scientist) proposed a tetrahedral structure for carbon atom in September of 1874. J. A. Le Bel (French scientist) published the same idea independently in November of 1874.
   1) van't Hoff was the first recipient of the Nobel Prize in Chemistry in 1901.
3. In 1877, Hermann Kolbe (of the University of Leipzig), one of the most eminent organic chemists of the time, criticized van't Hoff's publication on "The Arrangements of Atoms in Space." as a childish fantasy.
   1) He finds it more convenient to mount his Pegasus (飛馬座) (evidently taken from the stables of the Veterinary College) and to announce how, on his bold flight to Mount Parnassus (希臘中部的山;詩壇), he saw the atoms arranged in space.
4. The following information led van't Hoff and Le Bel to the conclusion that the

spatial orientation of groups around carbon atoms is tetrahedral.

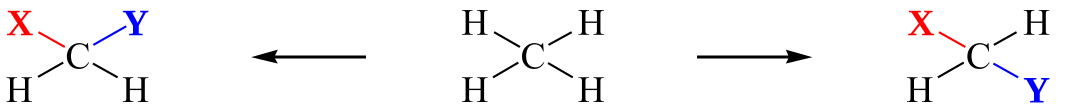
1) Only one compound with the general formula CH_3X is ever found.

2) Only one compound with the formula CH_2X_2 or CH_2XY is ever found.

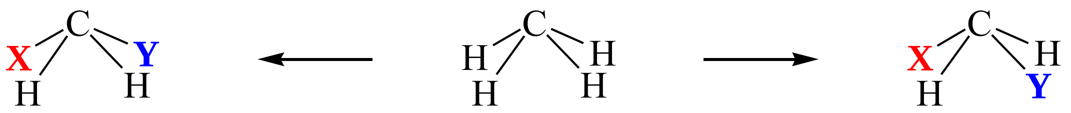
3) Two enantiomeric compounds with the formula CHXYZ are found.



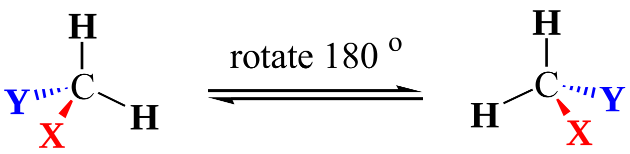
Planar Pyramidal Tetrahedral

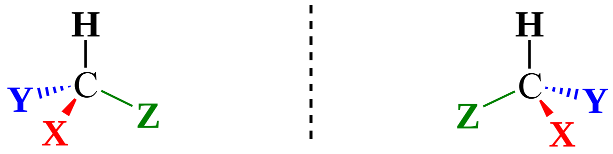


Cis *Trans*



Cis *Trans*





5.5 Tests for Chirality: Planes of Symmetry

1. Superposibility of the models of a molecule and its mirage:

   1) If the models are superposable, the molecule that they represent is **achiral**.

   2) If the models are nonsuperposable, the molecules that they represent are **chiral**.

2. The **presence** of **a *single* tetrahedral stereocenter** ⇒ **chiral molecule**.

3. The **presence** of **a plane of symmetry** ⇒ **achiral molecule**

   1) A **plane of symmetry** (also called a **mirror plane**) is ***an imaginary plane that***

bisects a molecule in such a way that the two halves of the molecule are mirror images of each other.

2) The plane may pass through atoms, between atoms, or both.

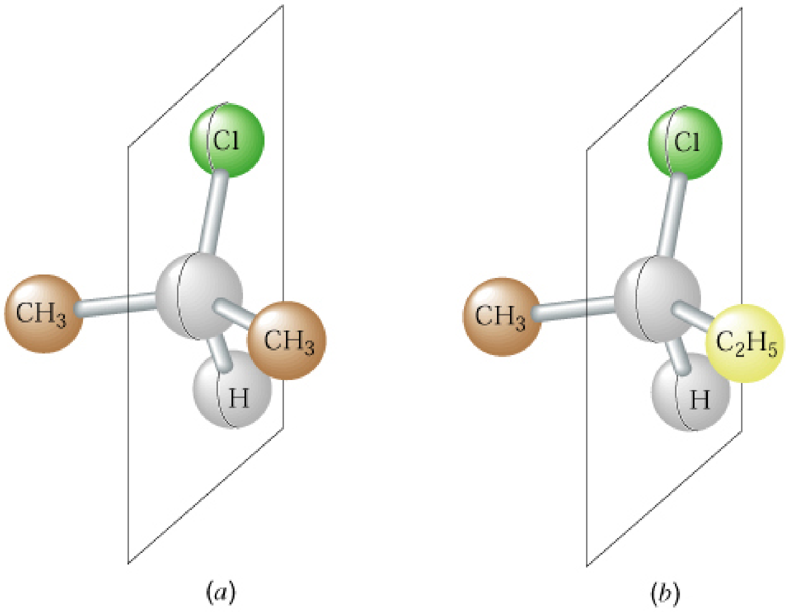
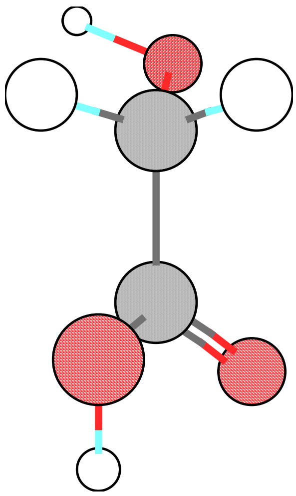


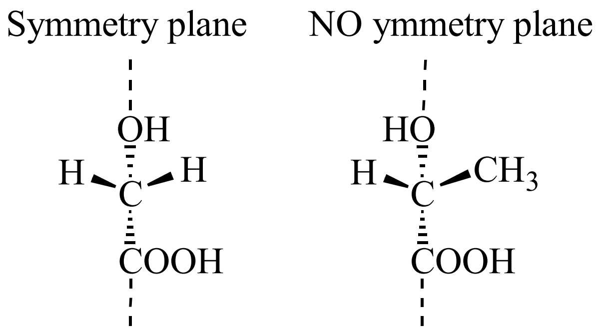
Figure 5.8 (a) 2-Chloropropane has a plane of symmetry and is achiral. (b) 2-Chlorobutane does not possess a plane of symmetry and is chiral.

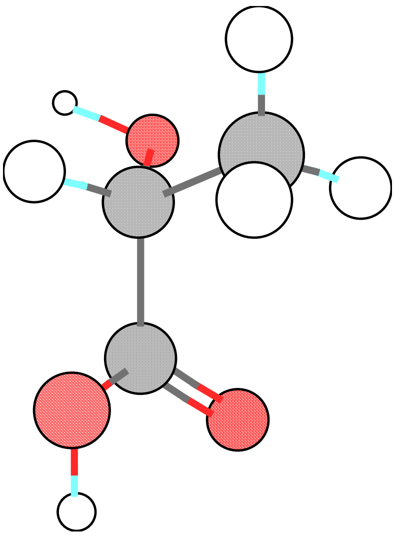
4. The **achiral** hydroxyacetic acid molecule versus the **chiral** lactic acid molecule:

1) Hydroxyacetic acid **has a plane of symmetry** that makes one side of the molecule a mirror image of the other side.

2) Lactic acid, however, **has no such symmetry plane**.





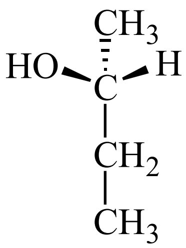


$HO–CH_2COOH$ | $CH_3CH(OH)COOH$
Hydroxyacetic acid | Lactic acid
(achiral) | (chiral)

5.6 Nomenclature of Enantiomers: The (*R*-*S*) System

5.6A Designation of Stereocenter

1. 2-Butanol (*sec*-Butyl alcohol):



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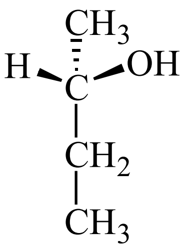


II

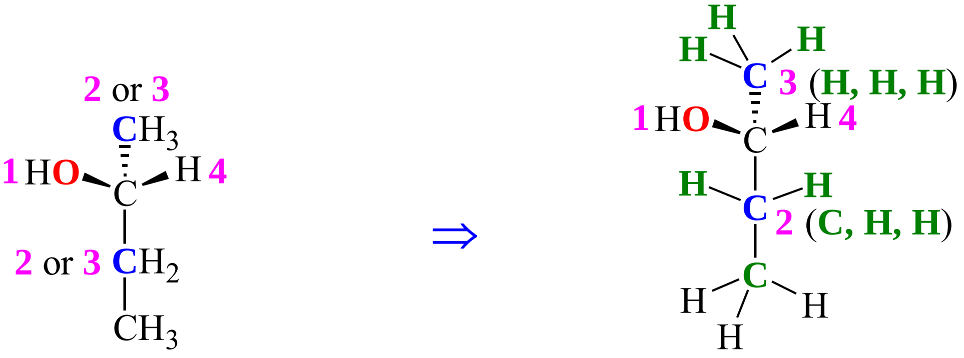
1) R. S. Cahn (England), C. K. Ingold (England), and V. Prelog (Switzerland) devised the (*R*–*S*) system (**Sequence rule**) for designating the configuration of chiral carbon atoms.
2) (*R*) and (*S*) are from the Latin words *rectus* and *sinister*:
   - i) *R* configuration: clockwise (*rectus*, "**right**")
   - ii) *S* configuration: counterclockwise (*sinister*, "**left**")

2. **Configuration:** the absolute stereochemistry of a **stereocenter**.

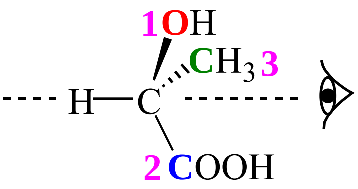
5.6B The (R-S) System: (Cahn-Ingold-Prelog System)

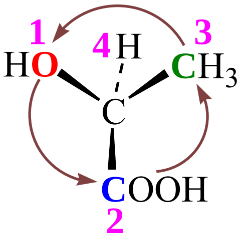
1. Each of the four groups attached to the **stereocenter** is assigned a **priority**.
   1) Priority is first assigned on the basis of the **atomic number** of the atom that is directly attached to the stereocenter.
   2) The group with the **lowest atomic number** is given the **lowest priority**, **4**; the group with **next higher atomic number** is given the **next higher priority**, **3**; and so on.
   3) In the case of isotopes, the isotope of greatest atomic mass has highest priority.
2. Assign a priority at the **first point of difference**.
   1) When a priority cannot be assigned on the basis of the atomic number of the

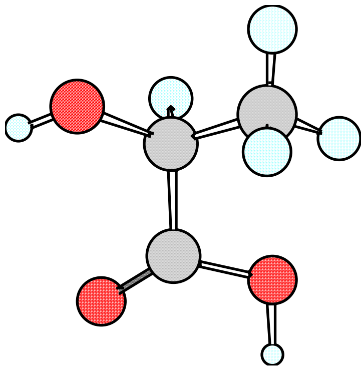
atoms that are diredtly attached to the stereocenter, then the next set of atoms in the unassigned groups are examined.



3. View the molecule with the group of lowest priority pointing away from us.
   1) If the direction from highest priority (4) to the next highest (3) to the next (2) is **clockwise**, the enantiomer is designated *R*.
   2) If the direction is **counterclockwise**, the enantiomer is designated *S*.

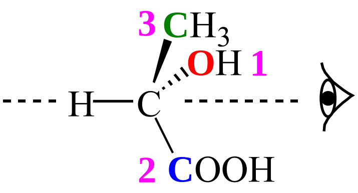


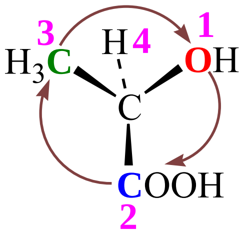


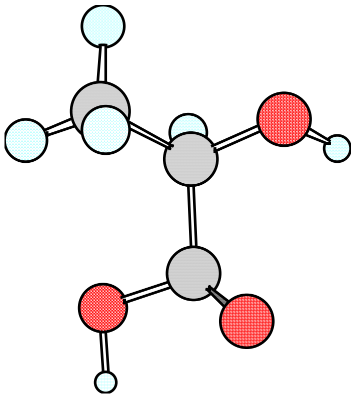


(*L*)-(+)-Lactic acid

***S* configuration (left turn on steering wheel)**



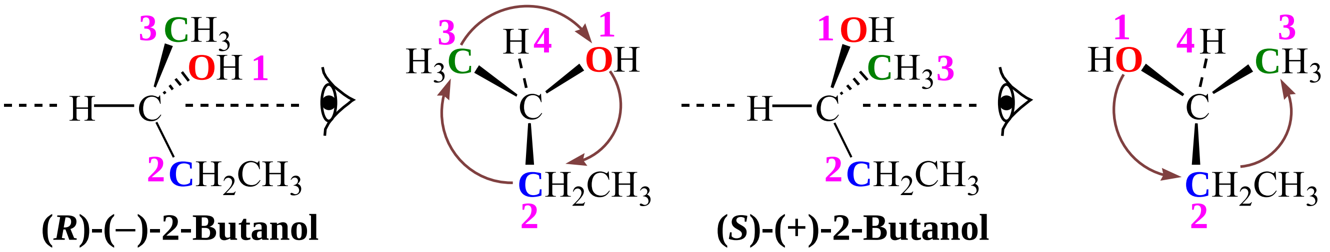




(*D*)-(–)-Lactic acid

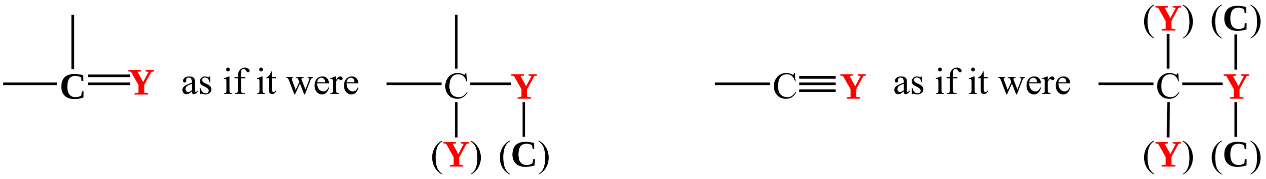
***R* configuration (right turn on steering wheel)**

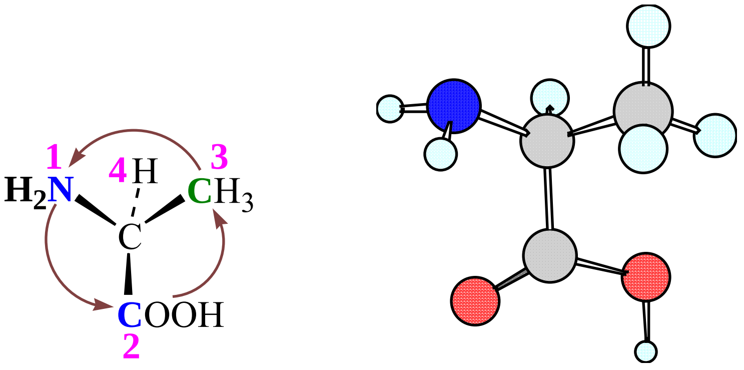
Assignment of configuration to (*S*)-(+)-lactic acid and (*R*)-(–)-lactic acid



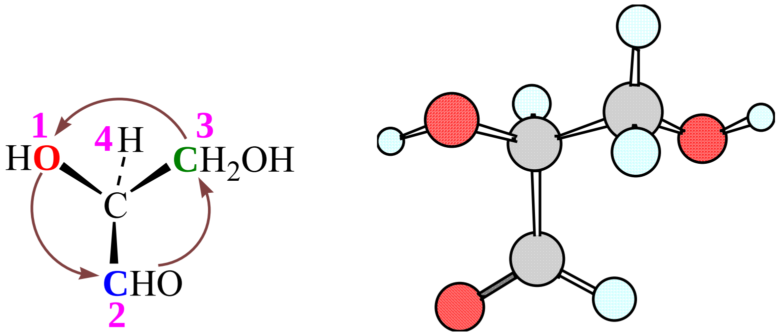
(*R*)-(–)-2-Butanol **(*S*)-(+)-2-Butanol**

4. **The sign of optical rotation is not related to the *R,S* designation**.
5. **Absolute configuration**:
6. Groups containing double or triple bonds are assigned priority as if both atoms were duplicated or triplicated.





(*S*)-Alanine [(*S*)-(+)-2-Aminopropionic acid], $[\alpha]_D$ = +8.5°



(*S*)-Glyceraldehyde [(*S*)-(–)-2,3-dihydroxypropanal], $[\alpha]_D$ = –8.7°

Assignment of configuration to (+)-alanine and (–)-glyceraldehyde:

Both happen to have the *S* configuration

5.7. PROPERTIES OF ENANTIOMERS: OPTICAL ACTIVITY

1. **Enantiomers** have ***identical*** **physical properties** such as boiling points, melting points, refractive indices, and solubilities in common solvents ***except*** **optical rotations**.
   1) Many of these properties are dependent on the magnitude of the intermolecular forces operating between the molecules, and for molecules that are mirror images of each other these forces will be identical.
   2) Enantiomers have **identical** **infrared** spectra, **ultraviolet** spectra, and **NMR** spectra if they are measured in **achiral** solvents.
   3) Enantiomers have **identical** **reaction rates** with **achiral** reagents.

Table 5.1 Physical Properties of (*R*)- and (*S*)-2-Butanol

Physical Property	(*R*)-2-Butanol	(*S*)-2-Butanol
Boiling point (1 atm)	99.5 °C	99.5 °C
Density (g mL^{-1} at 20 °C)	0.808	0.808
Index of refraction (20 °C)	1.397	1.397

2. **Enantiomers** show ***different*** **behavior** only when they ***interact*** with other **chiral substances**.
   1) Enantiomers show **different** **rates of reaction** toward other **chiral** molecules.
   2) Enantiomers show **different** **solubilities** in **chiral** solvents that consist of a single enantiomer or an excess of a single enantiomer.

3. Enantiomers rotate the plane of ***plane-polarized light*** in equal amounts ***but in opposite directions***.
   1) Separate enantiomers are said to be **optically active** compounds.

5.7A PLANE-POLARIZED LIGHT

1. A beam of light consists of two mutually perpendicular oscillating fields: **an oscillating electric field** and **an oscillating magnetic field**.

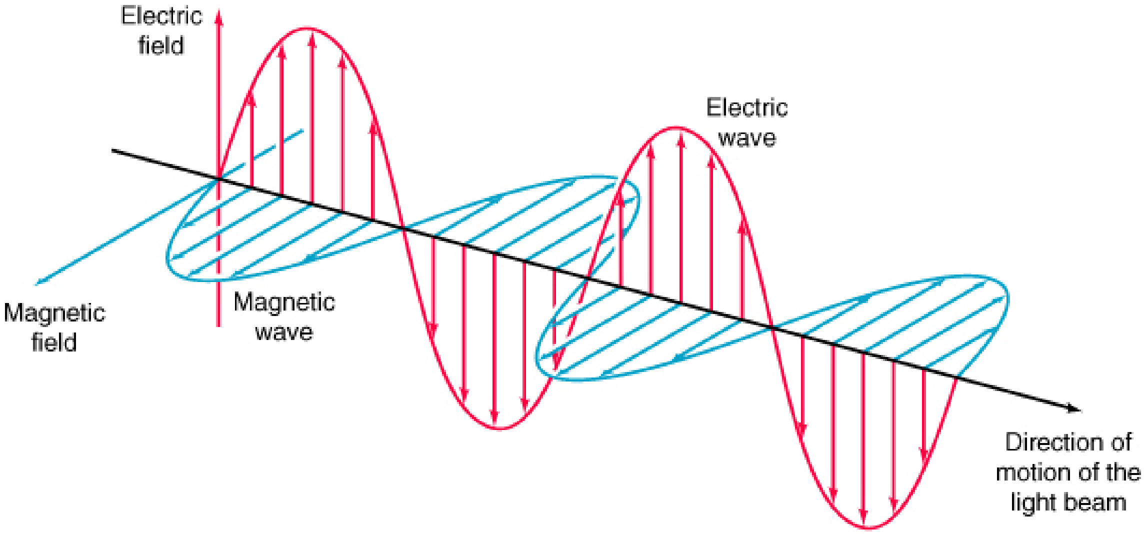


Figure 5.9 The oscillating electric and magnetic fields of a beam of ordinary light in one plane. The waves depicted here occur in all possible planes in ordinary light.

2. Oscillations of the **electric field** (and the **magnetic field**) are occurring in all possible planes **perpendicular** to the **direction of propagation**.

Figure 5.10 Oscillation of the electrical field of ordinary light occurs in all possible planes perpendicular to the direction of propagation.

3. **Plane-polarized light:**

1) When ordinary light is passed through a **polarizer**, the polarizer interacts with the electric field so that the electric field of the light emerges from the polarizer (and the magnetic field perpendicular to it) is **oscillating only in one plane**.

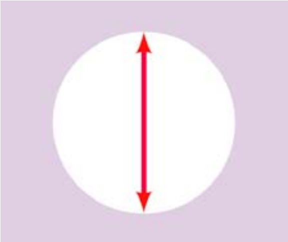


Figure 5.11 The plane of oscillation of the electrical field of plane-polarized light. In this example the plane of polarization is vertical.

4. The lenses of Polaroid sunglasses polarize light.

5.7B THE POLARIMETER

1. **Polarimeter:**

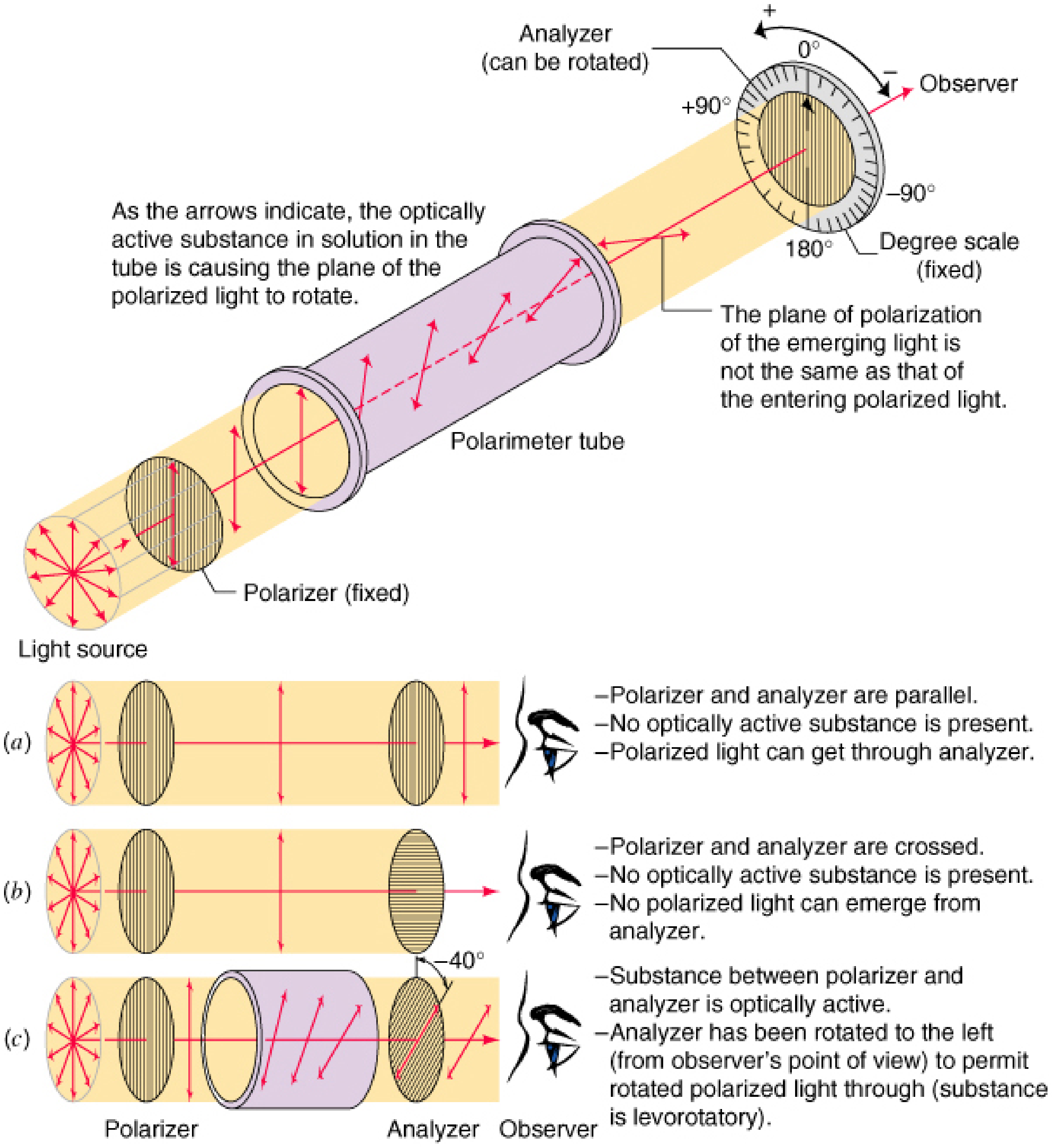


Figure 5.12 The principal working parts of a polarimeter and the measurement of optical rotation.

2. If the analyzer is rotated in a **clockwise** direction, the rotation, α (measured in

degree) is said to be **positive** (+), and if the rotation is **counterclockwise**, the rotation is said to be **negative** (–).

3. A substance that rotates plane-polarized light in the **clockwise** direction is said to be **dextrorotatory**, and one that rotates plane-polarized light in a **counterclockwise** direction is said to be **levorotatory** (Latin: *dexter*, right; and *laevus*, left).

5.7C SPECIFIC ROTATION: $[\alpha]_D^T$

1. **Specific rotation**, [α]**:**

$$[\alpha]_D^T = \frac{\alpha}{l \text{ x } c}$$

α: observed rotation

l: sample path length (dm)

c: sample concentration (g/mL)

$$[\alpha]_D^T = \frac{\text{Observed rotation, } \alpha}{\text{Path length, } l \text{ (dm) x Concentration of sample, } c \text{ (g/mL)}} = \frac{\alpha}{l \text{ x } c}$$

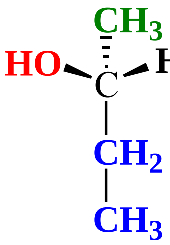
1) The specific rotation depends on the **temperature** and **wavelength** of light that is employed.

i) Na D-line: 589.6 nm = 5896 Å.

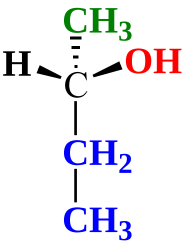
ii) Temperature (*T*).

2) The magnitude of rotation is dependent on the **solvent** when solutions are measured.

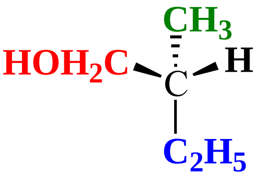
2. The **direction of rotation** of plane-polarized light is often incorporated into the names of optically active compounds**:**



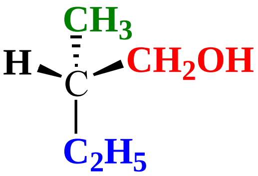
(*R*)-(–)-2-Butanol
$[\alpha]_D^{25}$ = **–13.52°**



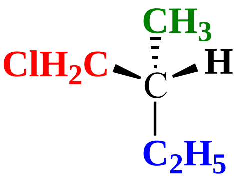
(*S*)-(+)-2-Butanol
$[\alpha]_D^{25}$ = **+13.52°**



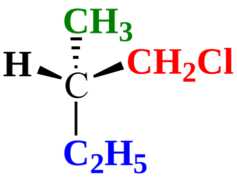
(*R*)-(+)-2-Methyl-1-butanol
$[\alpha]_D^{25}$ = **+5.756°**



(*S*)-(–)-2-Methyl-1-butanol
$[\alpha]_D^{25}$ = **–5.756°**



(*R*)-(–)-1-Chloro-2-methylbutane
$[\alpha]_D^{25}$ = **–1.64°**



(*S*)-(+)-1-Chloro-2-methylbutane
$[\alpha]_D^{25}$ = **+1.64°**

3. **No correlation exists between the configuration of enantiomers and the direction of optical rotation.**
4. **No correlation exists between the (*R*) and (*S*) designation and the direction of optical rotation.**
5. **Specific rotations of some organic compounds:**

Specific Rotations of Some Organic Molecules

Compound	$[\alpha]_D$ ***(degrees)***	***Compound***	$[\alpha]_D$ ***(degrees)***
Camphor	+44.26	Penicillin V	+223
Morphine	–132	Monosodium glutamate	+25.5
Sucrose	+66.47	Benzene	0
Cholesterol	–31.5	Acetic acid	0

5.8 THE ORIGIN OF OPTICAL ACTIVITY

1. Almost all ***individual*** molecules, **whether chiral or achiral**, are theoretically capable of **producing** a slight **rotation of the plane** of plane-polarized light.

   1) In a solution, many billions of molecules are in the path of the light beam and at any given moment these molecules are present in all possible directions.

   2) If the beam of plane-polarized light passes through a solution of an **achiral** compound:

      i) The effect of the first encounter might be to produce a very slight rotation of the plane of polarization to the right.

      ii) The beam should encounter at least one molecule that is in exactly the mirror image orientation of the first before it emereges from the solution.

      iii) The effect of the second encounter is to produce an equal and opposite rotation of the plane ⇒ **cancels the first rotation**.

      iv) Because so many molecules are present, it is **statistically** certain that ***for each encounter with a particular orientation there will be an encounter with a molecule that is in a mirror-image orientatio*** ⇒ **optically inactive**.

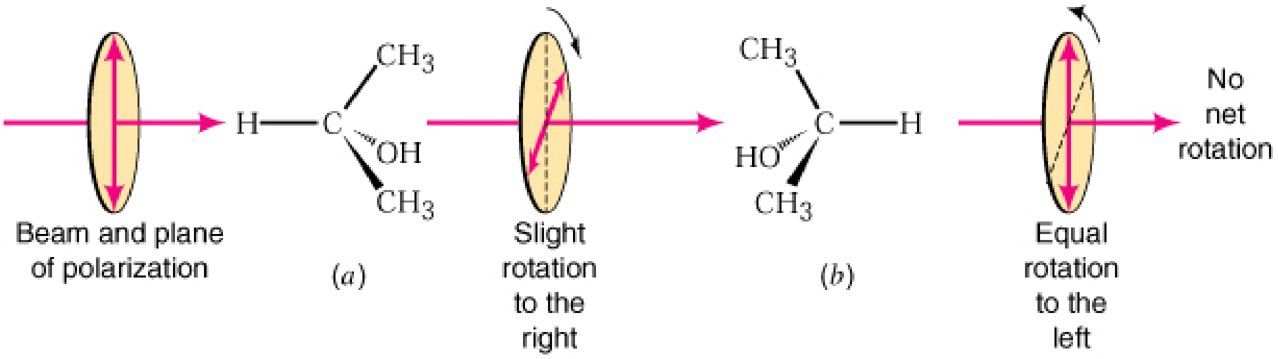


Figure 5.13 A beam of plane-polarized light encountering a molecule of 2-propanol (an achiral molecule) in orientation (a) and then a second molecule in the mirror-image orientation (b) The beam emerges from these two encounters with no net rotation of its plane of polarization.

   3) If the beam of plane-polarized light passes through a solution of a **chiral** compound:

      i) ***No molecule is present that can ever be exactly oriented as a mirror image of***

any given orientation of another molecule ⇒ **optically active**.

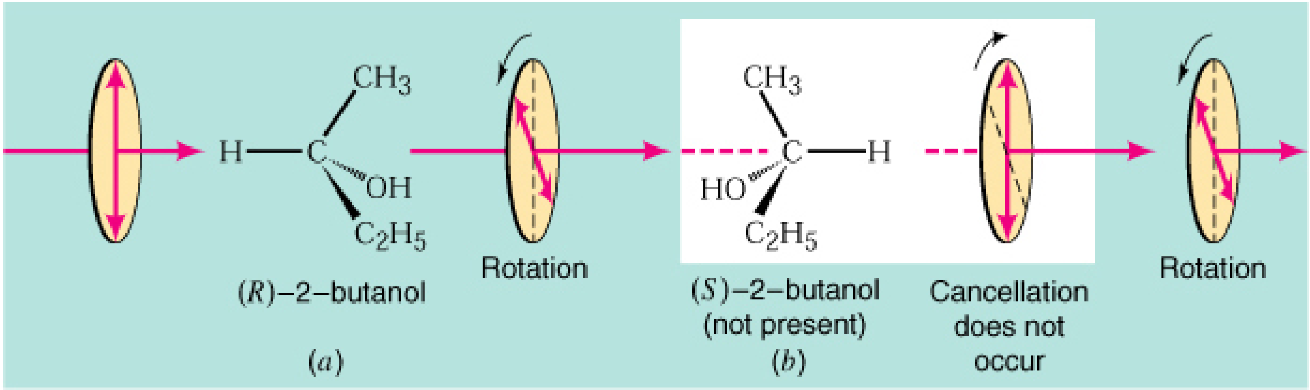


Figure 5.14 **(a) A beam of plane-polarized light encounters a molecule of (*R*)-2-butanol (a chiral molecule) in a particular orientation. This encounter produces a slight rotation of the plane of polarization. (b) exact cancellation of this rotation requires that a second molecule be oriented as an exact mirror image. This cancellation does not occur because the only molecule that could ever be oriented as an exact mirror image at the first encounter is a molecule of (*S*)-2-butanol, which is not present. As a result, a net rotation of the plane of polarization occurs.**

5.8A RACEMIC FORMS

1. A 50:50 mixture of the two chiral enantiomers.

5.8B RACEMIC FORMS AND ENANTIOMERIC EXCESS (e.e.)

$$\% \text{ Enantiomeric excess} = \frac{M_+ - M_-}{M_+ + M_-} \times 100$$

Where M+ is the mole fraction of the dextrorotatory enantiomer, and M_- the mole fraction of the levorotatory one.

$$\% \text{ optical purity} = \frac{[\alpha]_{\text{mixture}}}{[\alpha]_{\text{pure enantiomer}}} \times 100$$

1. $[\alpha]_{\text{pure enantiomer}}$ value has to be available
2. detection limit is relatively high (required large amount of sample for small rotation compounds)

5.11 MOLECULES WITH MORE THAN ONE STEREOCENTER

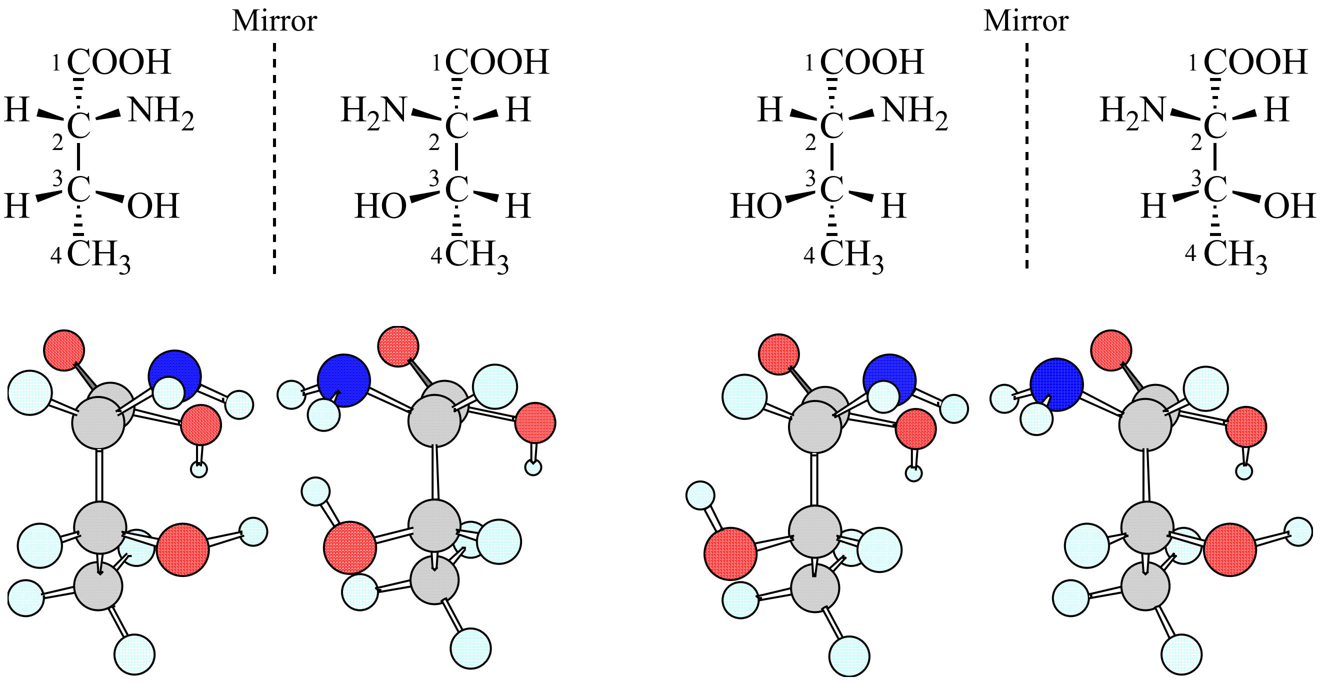
1. DIASTEREOMERS

1. Molecules have more than one stereogenic (chiral) center: **diastereomers**
2. **Diastereomers** are stereoisomers that are not mirror images of each other.

Relationships between four stereoisomeric threonines

Stereoisomer	*Enantiomeric with*	*Diastereomeric with*
2*R*,3*R*	2*S*,3*S*	2*R*,3*S* and 2*S*,3*R*
2*S*,3*S*	2*R*,3*R*	2*R*,3*S* and 2*S*,3*R*
2*R*,3*S*	2*S*,3*R*	2*R*,3*R* and 2*S*,3*S*
2*S*,3*R*	2*R*,3*S*	2*R*,3*R* and 2*S*,3*S*

3. Enatiomers must have opposite (mirror-image) configurations at *all* stereogenic centers.



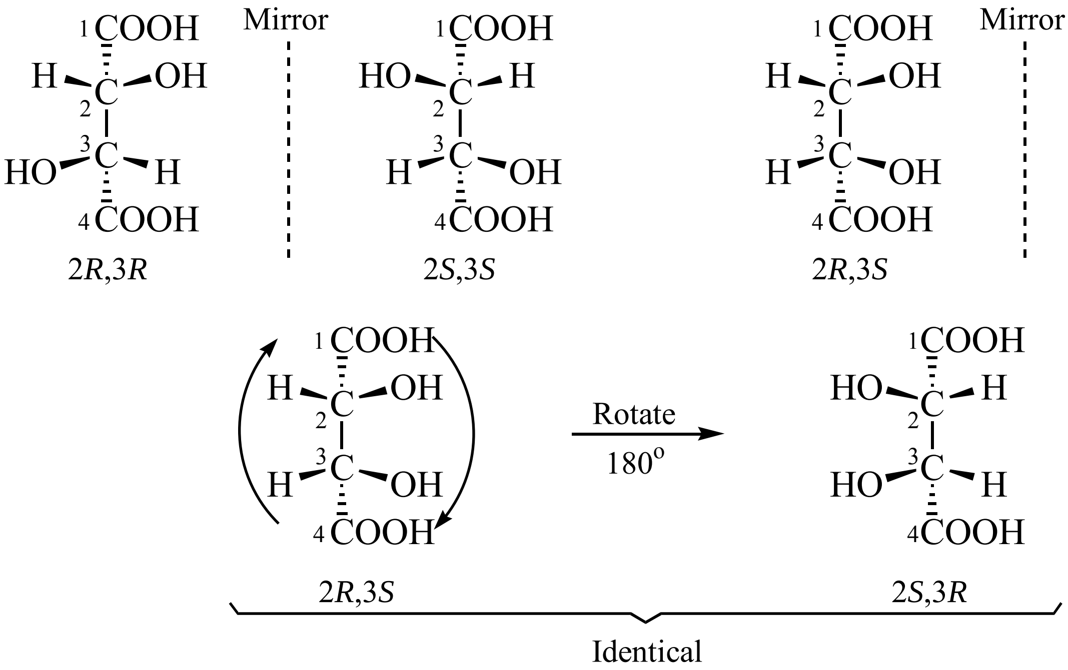
2*R*,3*R* 2*S*,3*S*
Enantiomers

2*R*,3*S* 2*S*,3*R*
Enantiomers

The four diastereomers of threonine (2-amino-3-hydroxybutanoic acid)

4. Diastereomers must have opposite configurations at *some* (one or more) stereogenic centers, but the same configurations at other stereogenic centers

5.11A Meso Compounds



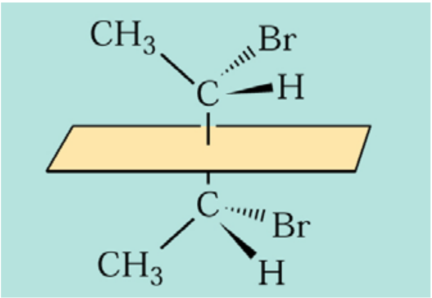


Figure 5.16 The plane of symmetry of *meso*-2,3-dibromobutane. This plane divides the molecule into halves that are mirror images of each other.

5.11B Naming Compounds with More Than One Stereocenter

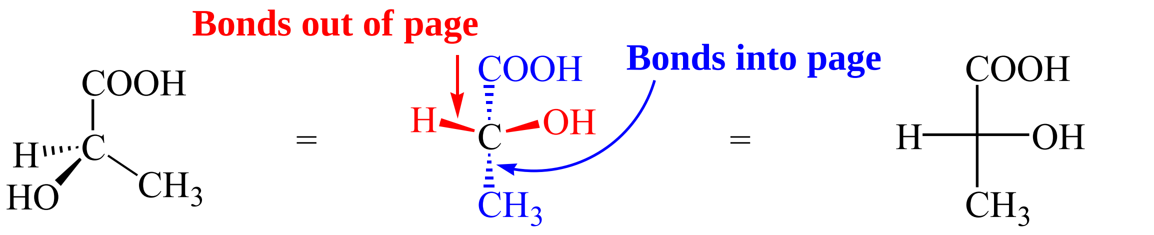
5.12 Fischer Projection Formulas

5.12A FISCHER PROJECTION (Emil Fischer, 1891)

1. **Convention:** The carbon chain is drawn along the vertical line of the Fischer projection, usually with the most highly oxidized end carbon atom at the top.

   1) **Vertical lines**: bonds going into the page.

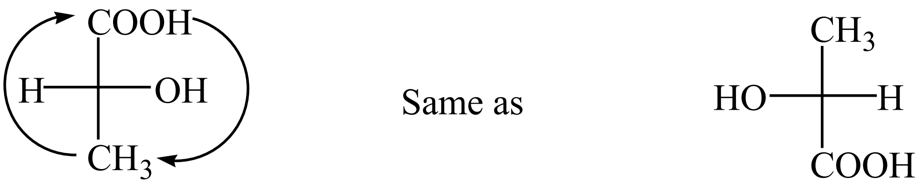
   2) **Horizontal lines**: bonds coming out of the page



(*R*)-Lactic acid **Fischer projection**

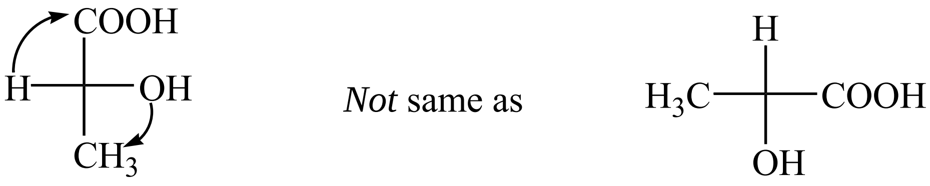
5.12B ALLOWED MOTIONS FOR FISCHER PROJECTION:

1. **180° rotation** (not 90° or 270°)**:**

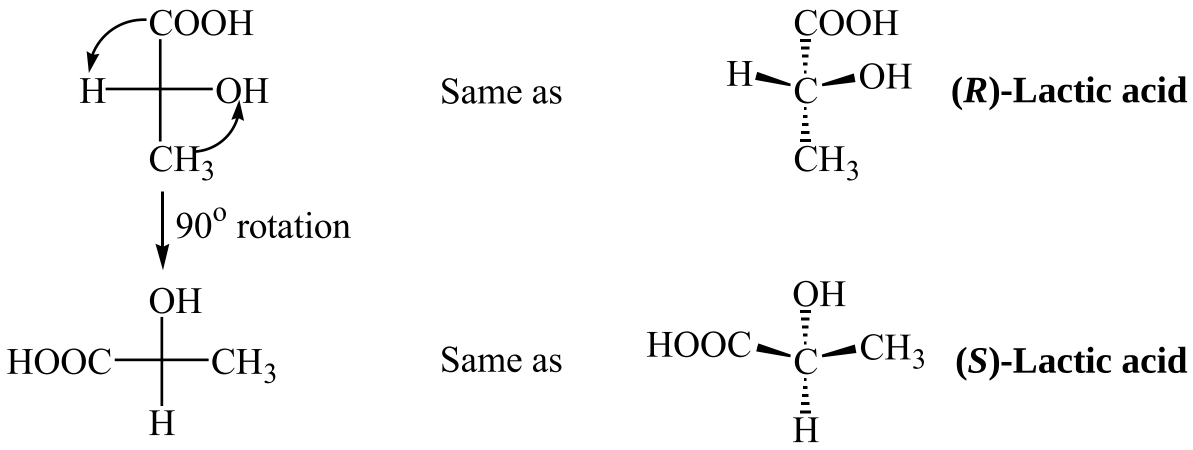


–COOH and –CH_3 go into plane of paper in both projections;
–H and –OH come out of plane of paper in both projections.

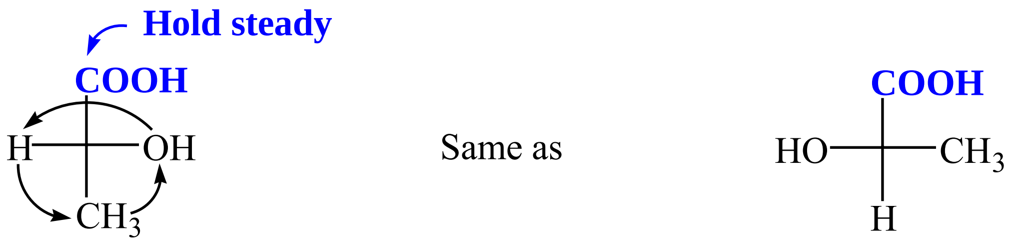
2. **90° rotation:** Rotation of a Fischer projection by 90° inverts its meaning.



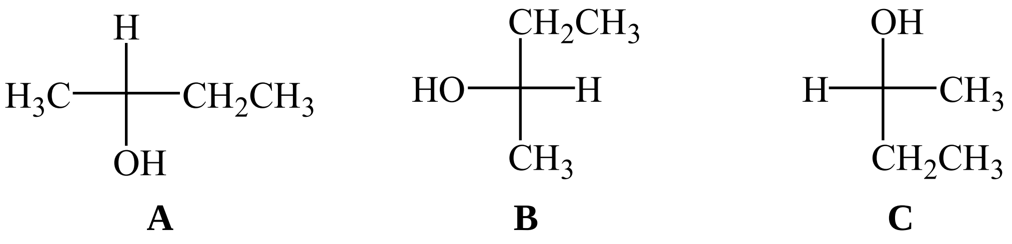
–COOH and –CH_3 go into plane of paper in one projection
but come out of plane of paper in other projection.

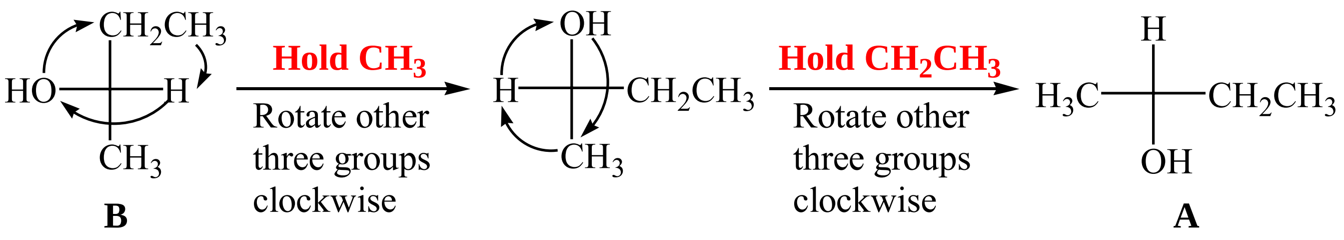


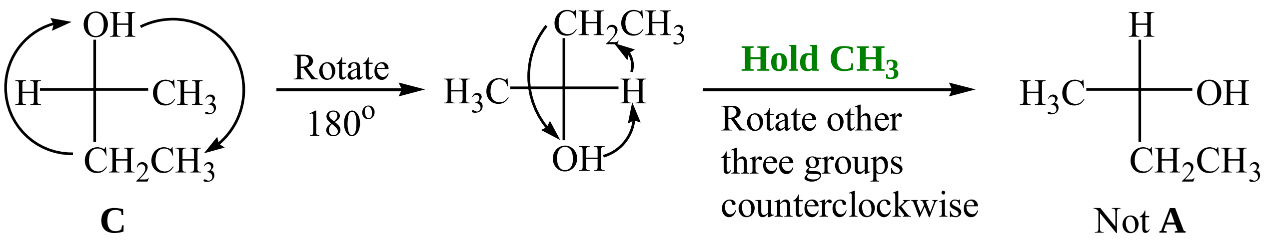
3. One group hold steady and the other three can rotate:



4. Differentiate different Fischer projections:

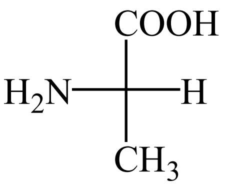




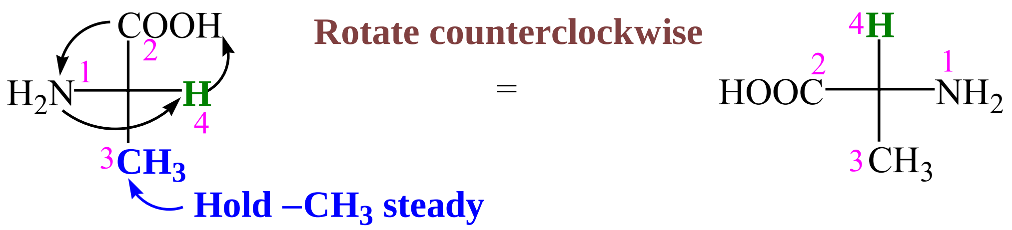


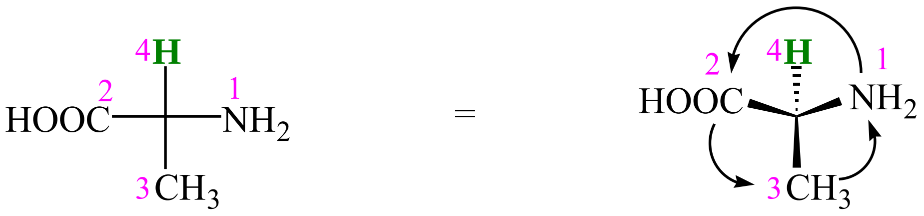
5.12C Assigning *R,S* Configurations to Fischer Projections:

1. Procedures for assigning *R,S* designations:
   1) Assign priorities to the four substituents.
   2) Perform one of the two allowed motions to place the group of lowest (fourth) priority at the top of the Fischer projection.
   3) Determine the direction of rotation in going from priority 1 to 2 to 3, and assign *R* or *S* configuration.

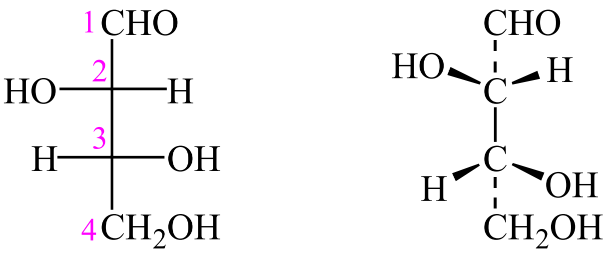


Serine





S stereochemistry



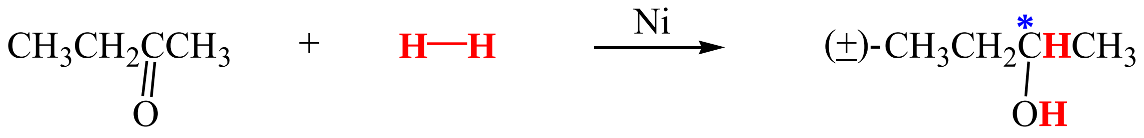
Threose [(2*S*,3*R*)-2,3,4-Trihydroxybutanal]

5.9 The Synthesis of Chiral Molecules

5.9A Racemic Forms

1. Optically active product(s) requires chiral reactants, reagents, and/or solvents:
   1) In cases that chiral products are formed from achiral reactants, racemic mixtures of products will be produced in the absence of chiral influence (reagent, catalyst, or solvent).

2. Synthesis of 2-butanol by the nickel-catalyzed hydrogenation of 2-butanone:



2-Butanone (achiral molecule) **Hydrogen (achiral molecule)** **(±)-2-Butanol [chiral molecules but 50:50 mixture (*R*) and (*S*)]**

3. Transition state of nickel-catalyzed hydrogenation of 2-butanone:

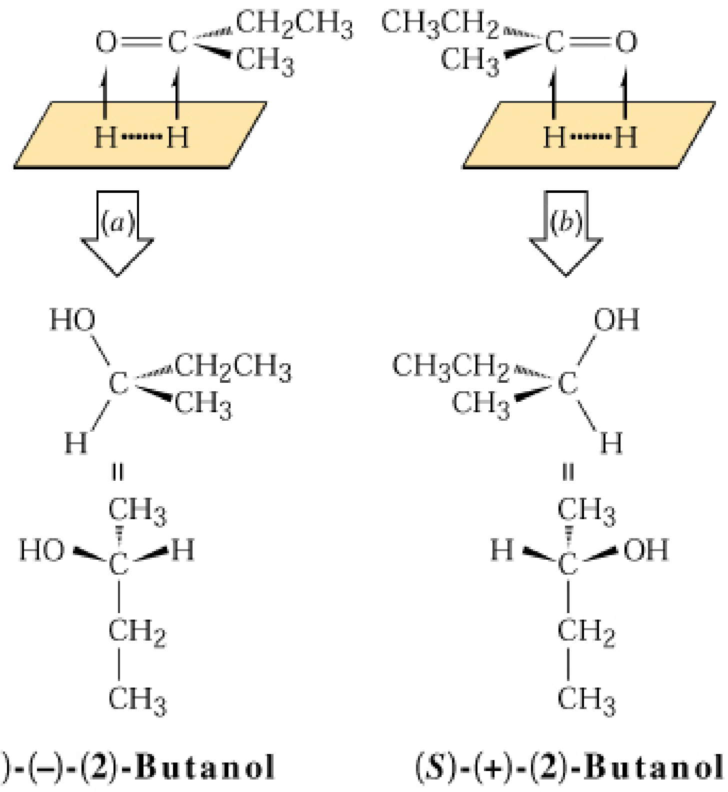
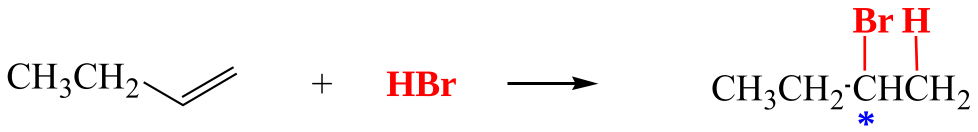


Figure 5.15 The reaction of 2-butanone with hydrogen in the presence of a nickel catalyst. The reaction rate by path (a) is equal to that by path (b).

(*R*)-(–)-2-butanol and (*S*)-(+)-2-butanol are produced in equal amounts, as a racemate.

4. Addition of HBr to 1-butene:



1-Butene (chiral) **(±)-2-Bromobutane (achiral)**

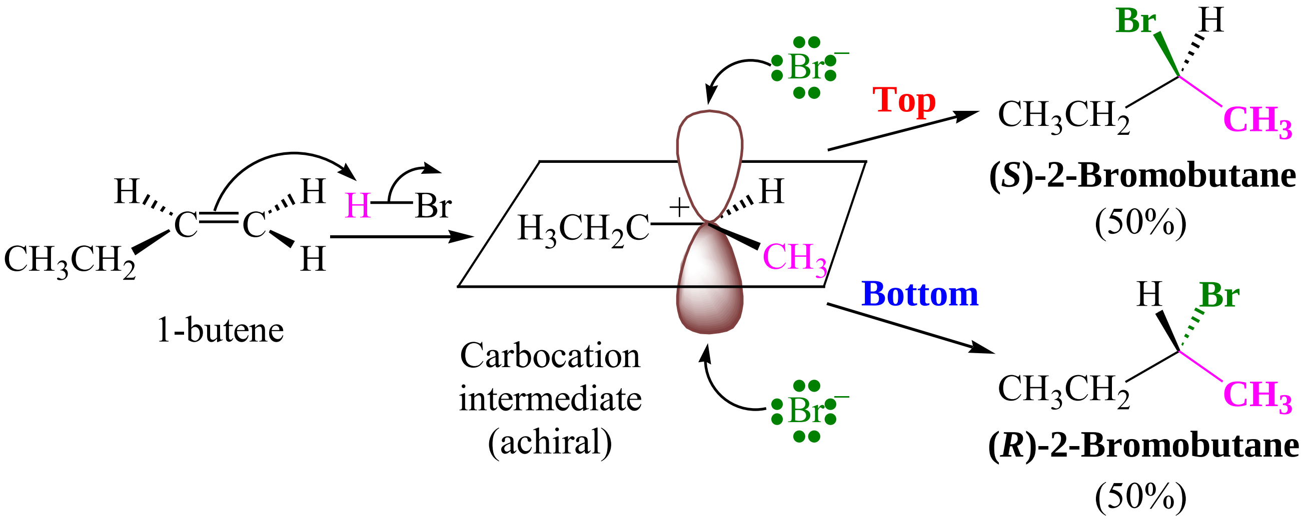
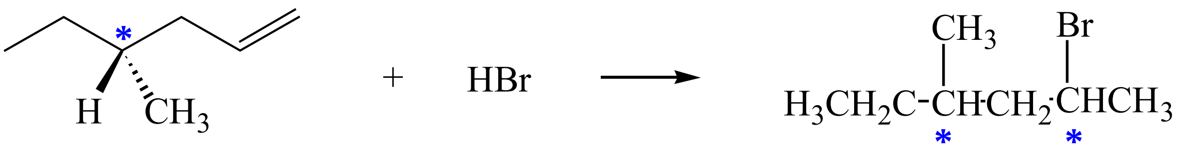
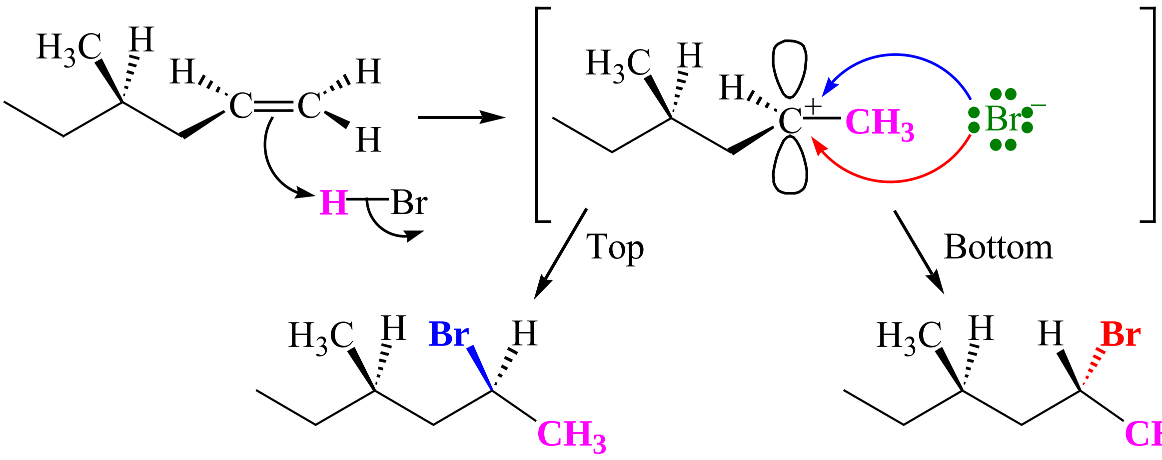


Figure 5. **Stereochemistry of the addition of HBr to 1-butene: the intermediate achiral carbocation is attacked equally well from both top and bottom, leading to a racemic product mixture.**



(*R*)-4-Methyl-1-hexene **2-Bromo-4-methylhexane**



(2*S*,4*R*)-2-Bromo-4-methylhexane **(2*R*,4*R*)-2-Bromo-4-methylhexane**

Figure 5. Attack of bromide ion on the 1-methylpropyl carbocation: Attack from the top leading to *S* products is the mirror image of attack from the bottom leading to *R* product. Since both are equally likely, racemic product is formed. The dotted C–Br bond in the transition state indicates partial bond formation.

5.9B ENANTIOSELECTIVE SYNTHESES

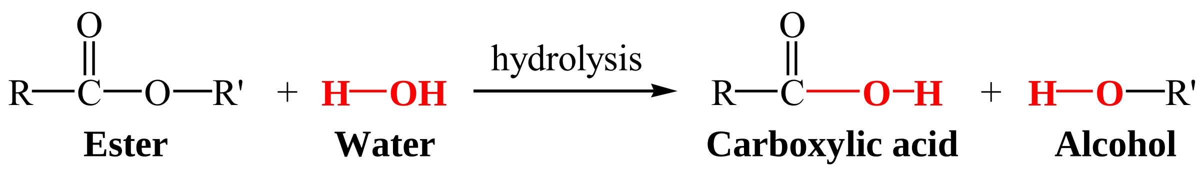
1. **Enantioselective:**
   1) In an **enantioselective** reaction, one enantiomer is produced predominantly over its mirror image.
   2) In an **enantioselective** reaction, a chiral reagent, catalyst, or solvent must assert an influence on the course of the reaction.

2. **Enzymes:**
   1) In nature, where most reactions are **enantioselective**, the chiral influences come from protein molecules called **enzymes**.
   2) **Enzymes** are biological catalysts of extraordinary efficiency.
      i) Enzymes not only have the ability to cause reactions to take place much more rapidly than they would otherwise, they also have the ability to assert a dramatic ***chiral influence*** on a reaction.
      ii) Enzymes possess an ***active site*** where the reactant molecules are bound, momentarily, while the reaction take place.
      iii) This ***active site*** is **chiral**, and **only one enantiomer** of a chiral reactant fits it

properly and is able to undergo reaction.

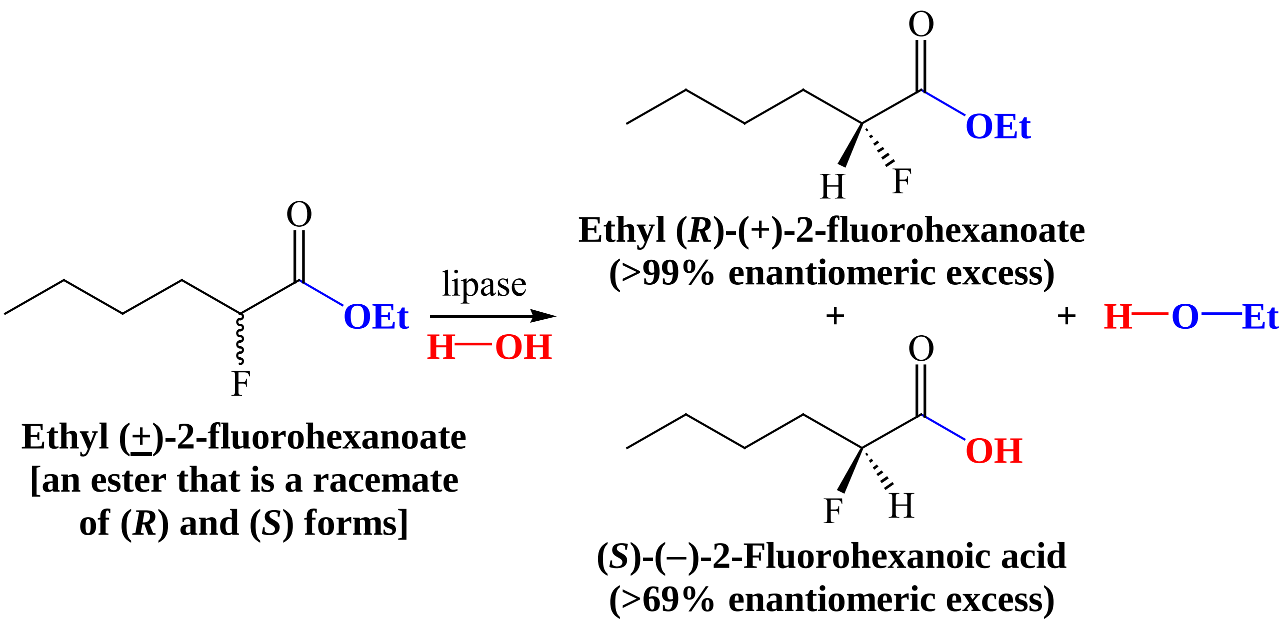
3. **Enzyme-catalyzed organic reactions:**

1) **Hydrolysis** of esters:



i) Hydrolysis, which means literally ***cleavage (lysis) by water***, can be carried out in a variety of ways that do not involve the use of enzyme.

2) **Lipase** catalyzes **hydrolysis** of esters:



i) Use of **lipase** allows the hydrolysis to be used to prepare almost pure enantiomers.

ii) The (*R*) enantiomer of the ester does not fit the active site of the enzyme and is, therefore, unaffected.

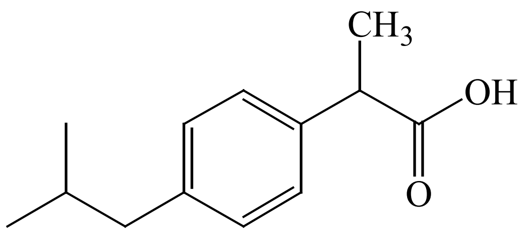
iii) Only the (*S*) enantiomer of the ester fits the active site and undergoes hydrolysis.

2) **Dehydrogenase** catalyzes **enantioselective reduction** of carbonyl groups.

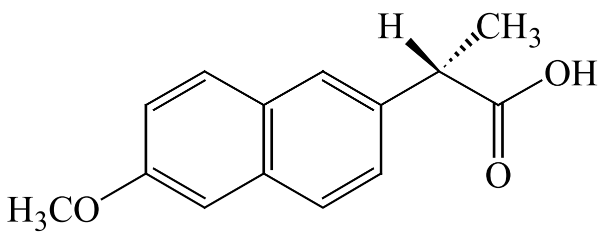
5.10 CHIRAL DRUGS

1. Chiral drugs over racemates:
   1) Of much recent interest to the pharmaceutical industry and the U.S. Food and Drug Administration (FDA) is the production and sale of "**chiral drugs**".
   2) In some instances, a drug has been marketed as a racemate for years even though only one enantiomer is the active agent.

2. **Ibuprofen** (Advil, Motrin, Nuprin): an anti-inflammatory agent



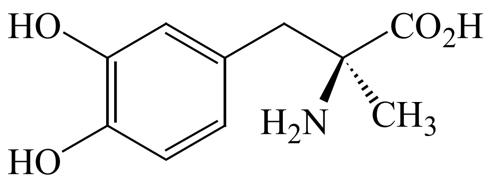
Ibuprofen



(*S*)-Naproxen

   1) Only the (*S*) enantiomer is active.
   2) The (*R*) enantiomer has no anti-inflammatory action.
   3) The (*R*) enantiomer is slowly converted to the (*S*) enantiomer in the body..
   4) A medicine based on the (*S*) isomer is along takes effect more quickly than the racemate.

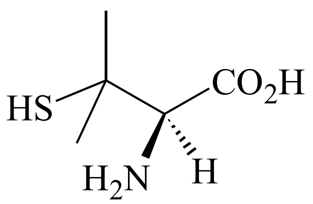
3. **Methyldopa** (Aldomet): an antihypertensive drug



(*S*)-Methyldopa

   1) Only the (*S*) enantiomer is active.

4. **Penicillamine**:



(*S*)-Penicillamine

1) The (*S*) isomer is a highly potent therapeutic agent for primary chronic arthritis.

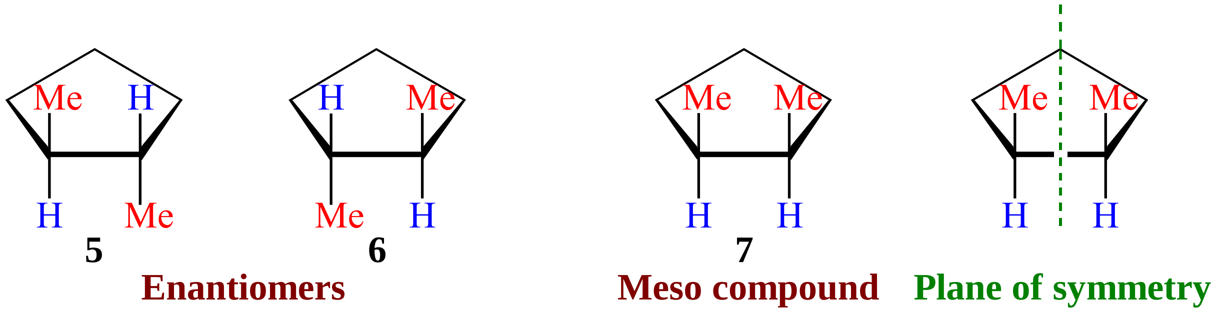
2) The (*R*) enantiomer has no therapeutic action, and it is highly toxic.

5. Enantiomers may have distinctively different effects.

1) The preparation of enantiomerically pure drugs is one factor that makes enantioselective synthesis and the resolution of racemic drugs (separation into pure enantiomers) active areas of research today.

5.13 STEREOISOMERISM OF CYCLIC COMPOUNDS

1. 1,2-Dimethylcyclopentane has two stereocenters and exists in three stereomeric forms **5**, **6**, and **7**.



1) The *trans* compound exists as a pair of enantiomers **5** and **6**.

2) *cis*-1,2-Dimethylcyclopentane has a plane of symmetry that is perpendicular to the plane of the ring and is a meso compound.

5.13A CYCLOHEXANE DERIVATIVES

1. **1,4-Dimethylcyclohexanes:** two ***isolable stereoisomers***

1) Both *cis*- and *trans*-1,4-dimethylcyclohexanes **have a symmetry plane** ⇒ **have no stereogenic centers** ⇒ **Neither *cis* nor *trans* form is chiral** ⇒ neither is optically active.

2) The *cis* and *trans* forms are diastereomers.

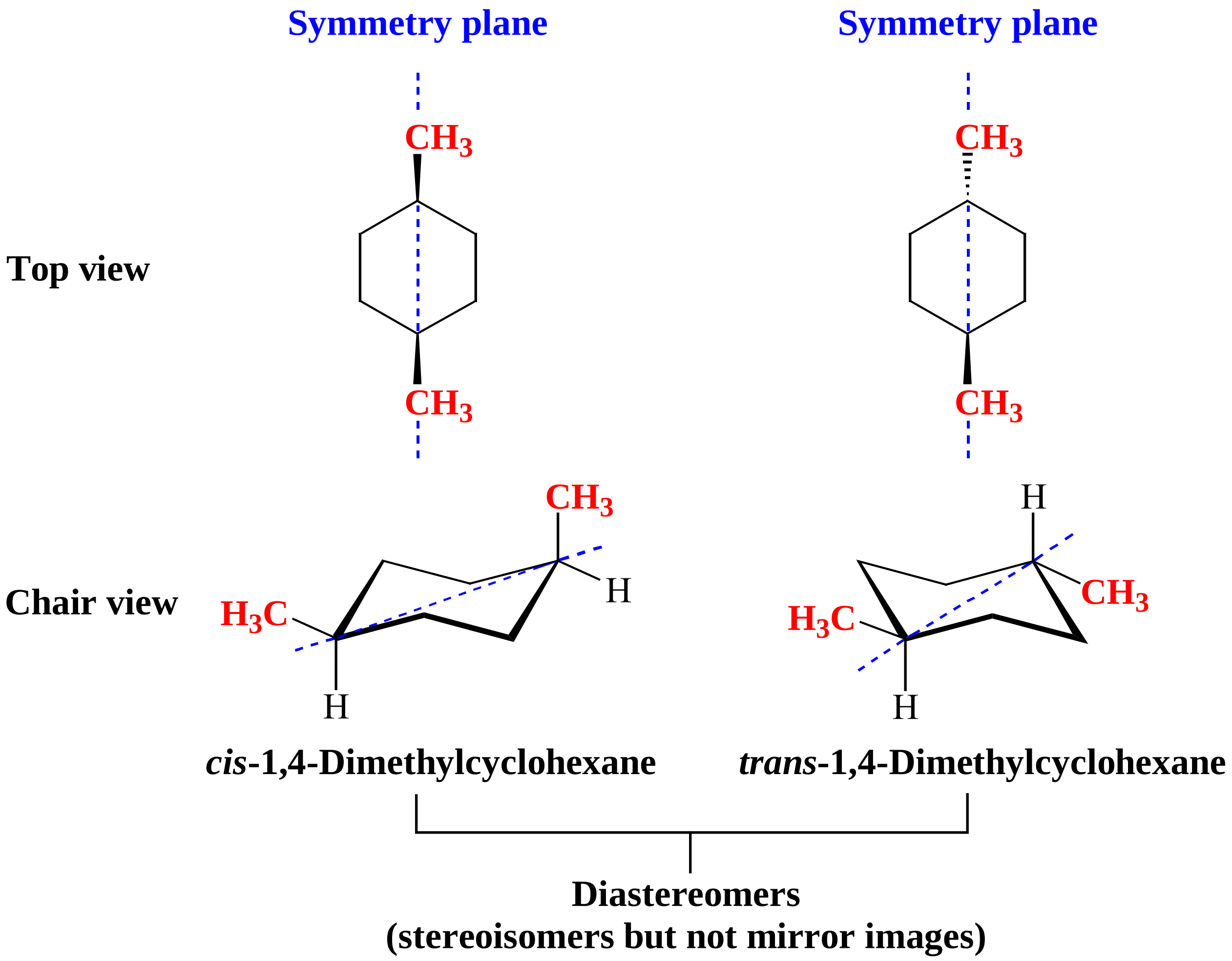


Figure 5.17 **The *cis* and *trans* forms of 1,4-dimethylcyclohexane are diastereomers of each other. Both compounds are achiral.**

2. **1,3-Dimethylcyclohexanes:** three ***isolable stereoisomers***

1) 1,3-Dimethylcyclohexane has two stereocenters ⇒ 4 stereoisomers are possible.

2) *cis*-1,3-Dimethylcyclohexane has a plane of symmetry and is achiral.

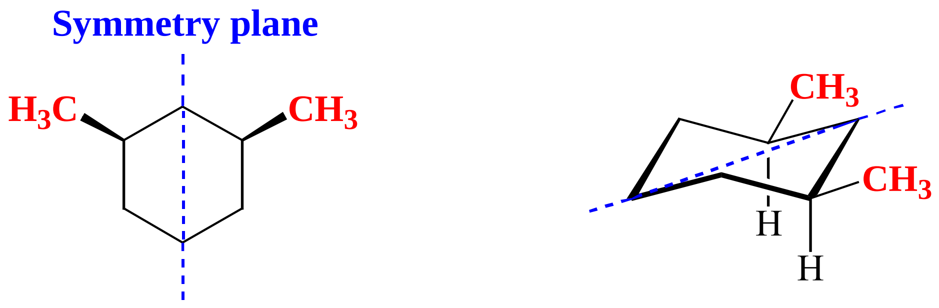


Figure 5.18 ***cis*-1,3-Dimethylcyclohexane has a plane of symmetry and is therefore achiral.**

3) *trans*-1,3-Dimethylcyclohexane does not have a plane of symmetry and exists as

a pair of enantiomers.

i) They are not superposable on each other.

ii) They are noninterconvertible by a ring-flip.

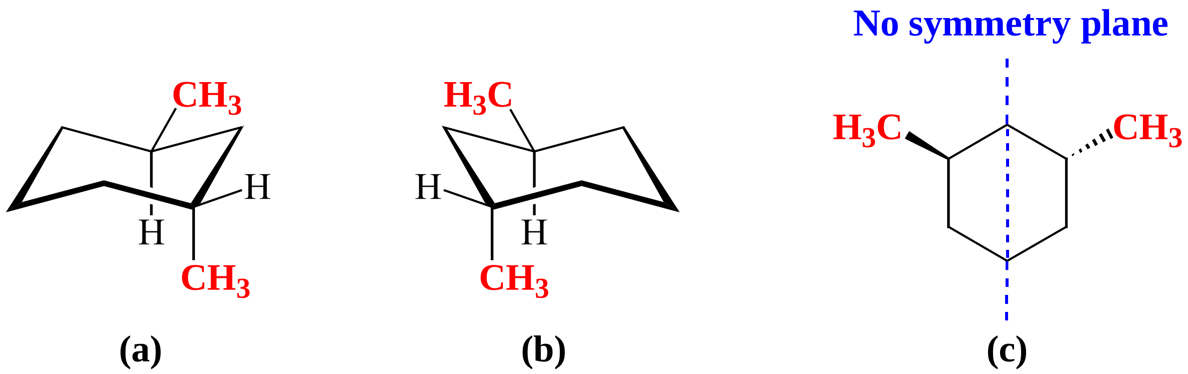
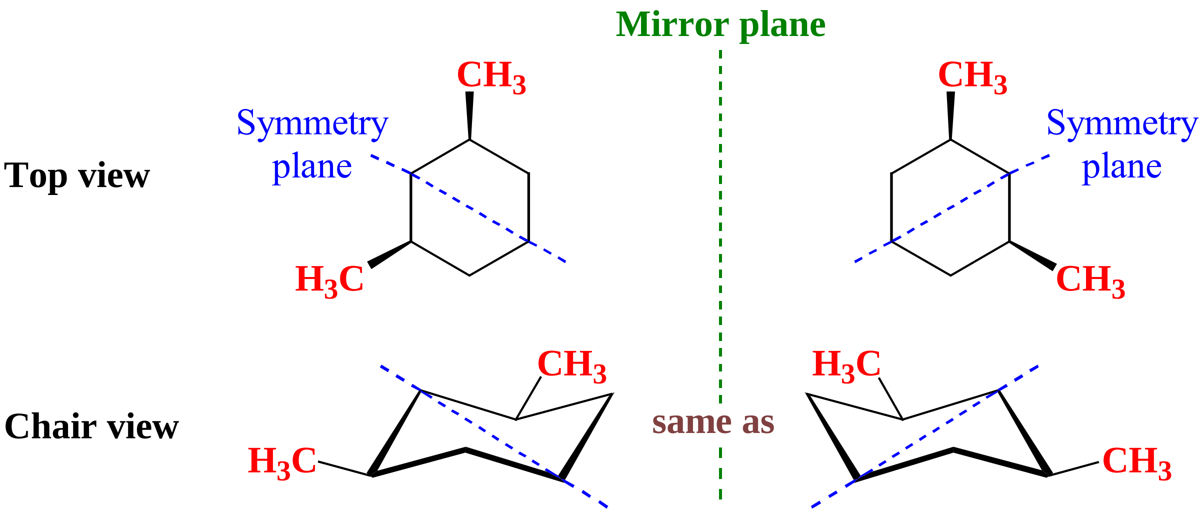
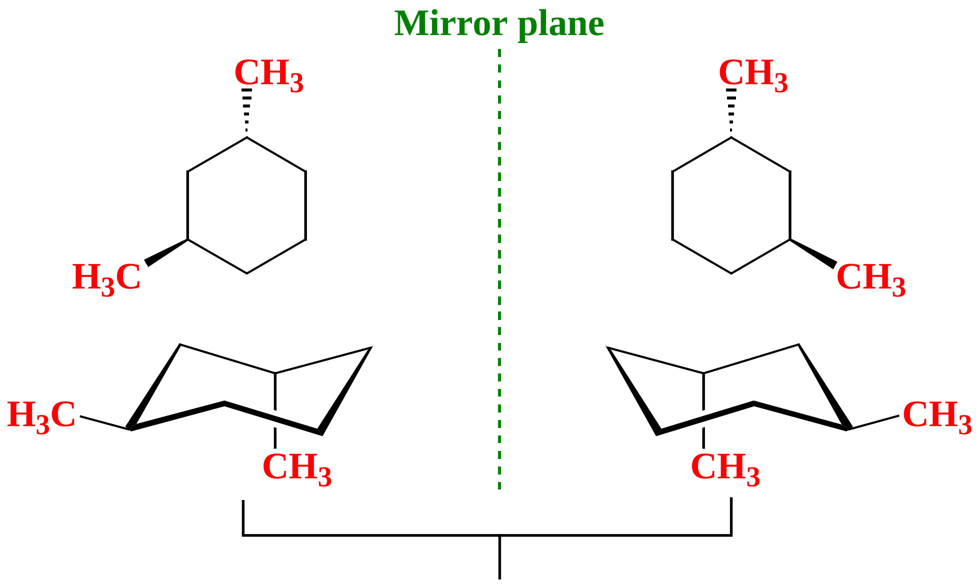


Figure 5.19 ***trans*-1,3-Dimethylcyclohexane does not have a plane of symmetry and exists as a pair of enantiomers. The two structures (*a* and *b*) shown here are not superposable as they stand, and flipping the ring of either structure does not make it superposable on the other. (*c*) A simplified representation of (*b*).**



Meso *cis*-1,3-dimethylcyclohexane



Enantiomers
(+)- and (–)-*trans*-1,3-Dimethylcyclohexane

3. **1,2-Dimethylcyclohexanes:** three *isolable stereoisomers*

1) 1,2-Dimethylcyclohexane has two stereocenters ⇒ 4 stereoisomers are possible.

2) *trans*-1,2-Dimethylcyclohexane has no plane of symmetry ⇒ exists as a pair of enantiomers.

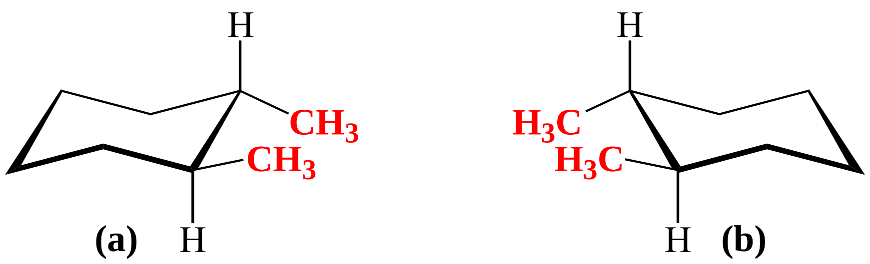


Figure 5.20 ***trans*-1,2-Dimethylcyclohexane has no plane of symmetry and exists as a pair of enantiomers (*a* and *b*). [Notice that we have written the most stable conformations for (*a*) and (*b*). A ring flip of either (*a*) or (*b*) would cause both methyl groups to become axial.]**

3) *cis*-1,2-Dimethylcyclohexane:

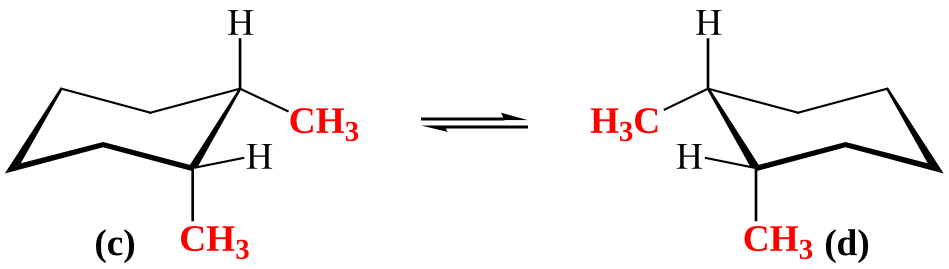


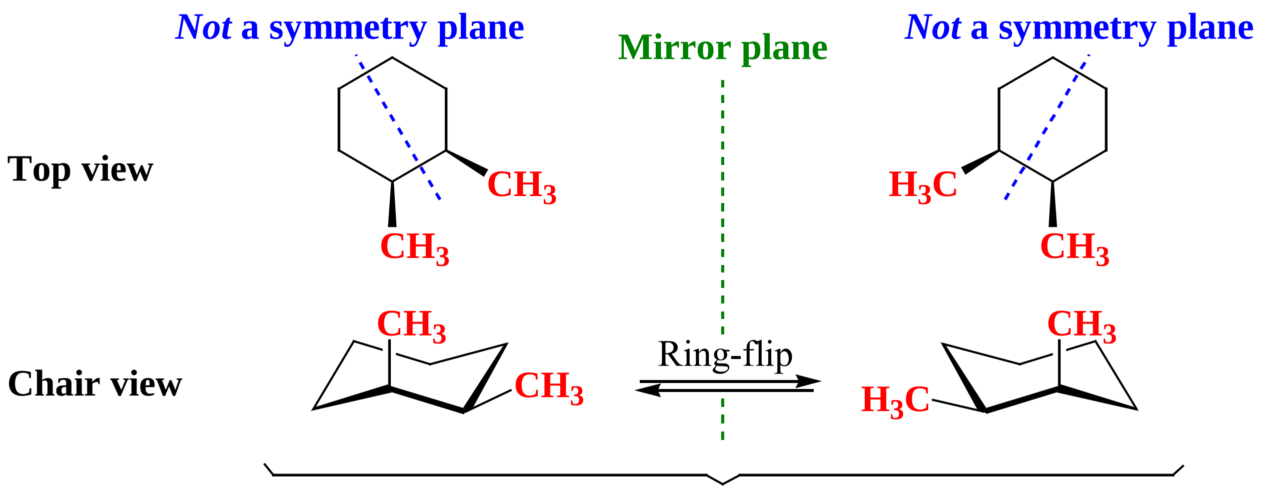
Figure 5.21 ***cis*-1,2-Dimethylcyclohexane exists as two rapidly interconverting chair conformations (*c*) and (*d*).**

i) The two conformational structures (*c*) and (*d*) are **mirror-image structures** but are **not identical**.

ii) Neither has a **plane of symmetry** ⇒ each is a **chiral molecule** ⇒ **they are *interconvertible* by a ring flip** ⇒ they **cannot be separated**.

iii) Structures (*c*) and (*d*) interconvert rapidly even at temperatures considerably below room temperature ⇒ they represent an interconverting **racemic form**.

iv) Structures (*c*) and (*d*) are not **configurational stereoisomers** ⇒ they are **conformational stereoisomers**.



***cis*-1,2-Dimethylcyclohexane**
(interconvertible enantiomers)

4. In general, it is possible to predict the presence or absence of optical activity in any substituted cycloalkane merely by looking at **flat structures**, without considering the exact three-dimensional chair conformations.

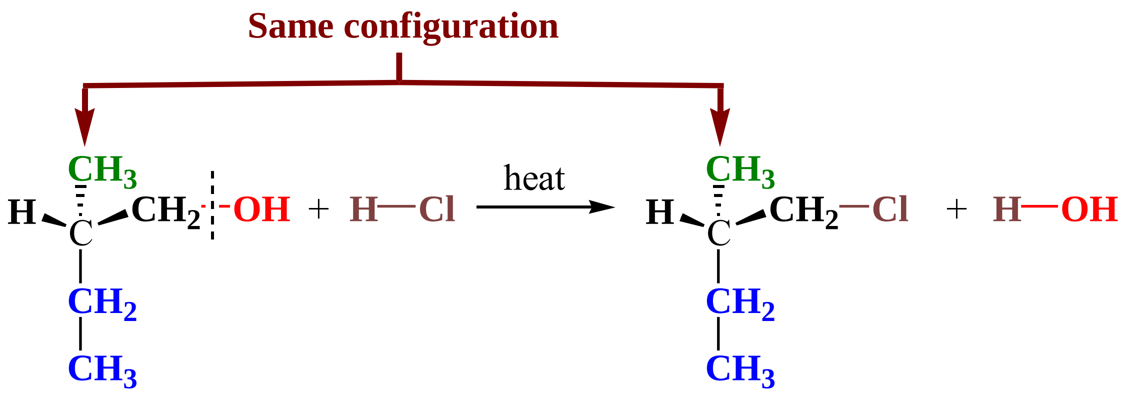
5.14 Relating Configurations through Reactions in which No Bonds to the Stereocenter are Broken

1. **Retention of configuration:**

1) If a reaction takes place **with no bond to the stereocenter is broken**, the product will have the **same configuration** of groups around the stereocenter as the reactant

2) The reaction proceeds with **retention of configuration**.

2. (*S*)-(–)-2-Methyl-1-butanol is heated with concentrated HCl:



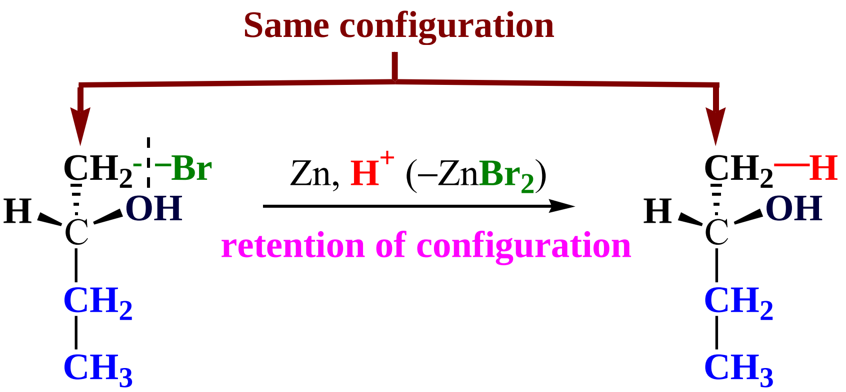
(*S*)-(–)-2-Methyl-1-butanol $[\alpha]_D^{25}$ = **–5.756°**

(*S*)-(+)-2-Methyl-1-butanol $[\alpha]_D^{25}$ = **+1.64°**

1) The product of the reaction must have the **same configuration** of groups around the stereocenter that the reactant had ⇒ comparable or identical groups in the two compounds occupy the same relative positions in space around the stereocenter.

2) While the (*R*-*S*) designation ***does not change*** [both reactant and product are (*S*)] the direction of optical rotation ***does change*** [the reactant is (–) and the product is (+)].

3. (*R*)-1-Bromo-2-butanol is reacted with Zn/H^+:



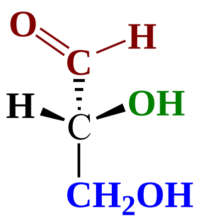
(*R*)-1-Bromo-2-butanol **(*S*)-2-butanol**

1) The (*R*-*S*) designation ***changes*** while the reaction proceeds with **retention of configuration**.
2) The product of the reaction has the same **relative configuration** as the reactant.

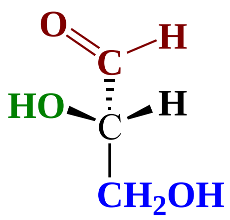
5.14A Relative and Absolute Configurations

1. Before 1951 only relative configuration of chiral molecules were known.
   1) No one prior to that time had been able to demonstrate with certainty what actual spatial arrangement of groups was in any chiral molecule.

2. CHEMICAL CORRELATION: configuration of chiral molecules were related to each other ***through reactions of known stereochemistry***.
3. **Glyceraldehyde**: the standard compound for chemical correlation of configuration.



and

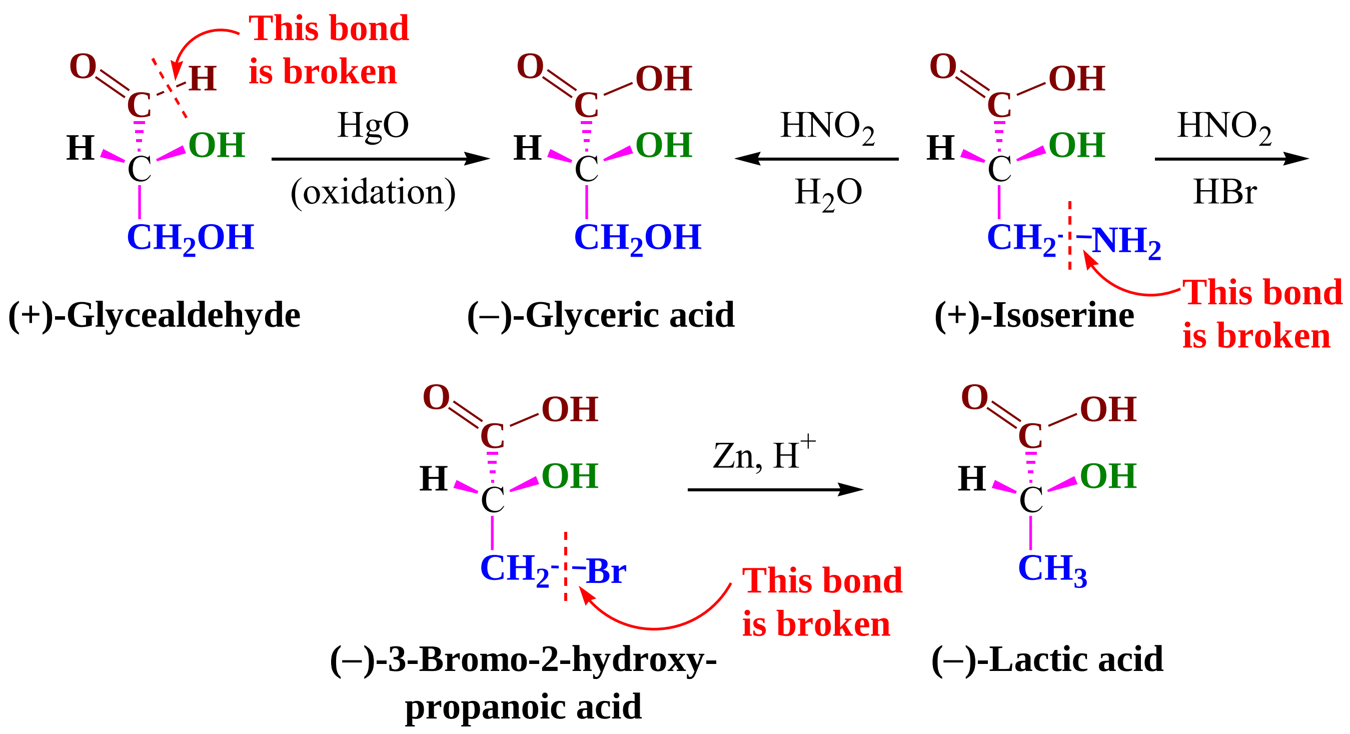


(*R*)-Glyceraldehyde
***D*-Glyceraldehyde**

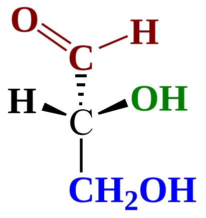
(*S*)-Glyceraldehyde
***L*-Glyceraldehyde**

1) One glyceraldehydes is dextrorotatory (+) and the other is levorotatory (–).
2) Before 1951 no one could be sure which configuration belonged to which enantiomer.
3) Emil Fischer arbitrarily assigned the (*R*) configuration to the (+)-enantiomer.
4) The configurations of other componds were related to glyceraldehydes through reactions of known stereochemistry.

4. The configuration of (–)-lactic acid can be related to (+)-glyceraldehyde through the following sequence of reactions:

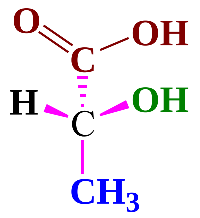


i) If the configuration of (+)-glyceraldehyde is as follows:



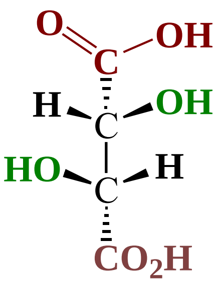
(*R*)-(+)-Glycealdehyde

ii) Then the configuration of (–)-lactic acid is:



(*R*)-(–)-Lactic acid

5. The configuration of (–)-glyceraldehyde was related through reactions of known stereochemistry to (+)-tartaric acid.



(+)-Tartaric acid

i) In 1951 J. M. Bijvoet, the director of the van't Hoff Laboratory of the University of Utrecht in the Netherlands, using X-ray diffraction, demonstrated conclusively that (+)-tartaric acid had the **absolute configuration** shown above.

6. The original arbitrary assignment of configurations of (+)- and (–)-glyceraldehyde was correct.

i) The configurations of all of the compounds that had been related to one glyceraldehyde enantiomer or the other were known with certainty and were now **absolute configurations**.

5.15 SEPARATION OF ENANTIOMERS: RESOLUTION

1. **How are enantiomers separated?**

1) Enantiomers have identical solubilities in ordinary solvents, and they have identical boiling points.

2) Conventional methods for separating organic compounds, such as crystallization and distillation, fail to separate racemic mixtures.

5.15A PASTEUR'S METHOD FOR SEPARATING ENANTIOMERS

1. Louis Pasteur: the founder of the field of stereochemistry.

1) Pasteur separated a racemic form of a salt of tartaric acid into two types of crystals in 1848 led to the discovery of enantioisomerism.

i) (+)-Tartaric acid is one of the by-products of wine making.

2. Louis Pasteur's discovery of enantioisomerism led, in 1874, to the proposal of the tetrahedral structure of carbon by van't Hoff and Le Bel.

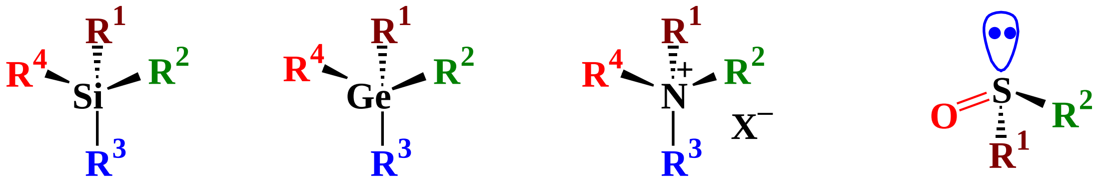
5.15B Current Methods for Resolution of Enantiomers

1. Resolution *via* **Diastereomer** Formation:
   1) Diastereomers, because they have **different melting points**, **different boiling points**, and **different solubilities**, can be separated by conventional methods..

2. Resolution *via* **Molecular Complexes**, **Metal Complexes**, and **Inclusion Compounds**:
3. **Chromatographic Resolution**:
4. **Kinetic Resolution**:

5.16 Compounds with Stereocenters Other Than Carbon

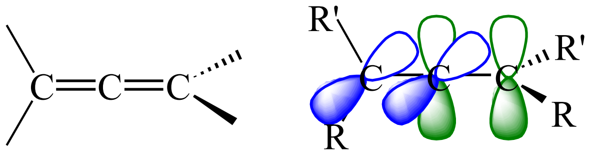
1. **Stereocenter:** any tetrahedral atom with four different groups attached to it.
   1) Silicon and germanium compounds with four different groups are **chiral** and the enantiomers can, in principle, be separated.



   2) Sulfoxides where one of the four groups is a nonbonding electron pair are **chiral**.
   3) Amines where one of the four groups is a nonbonding electron pair are **achiral** due to **nitrogen inversion**.

5.17 CHIRAL MOLECULES THAT DO NOT POSSES A TETRAHEDRAL ATOM WITH FOUR DIFFERENT GROUPS

1. **Allenes:**



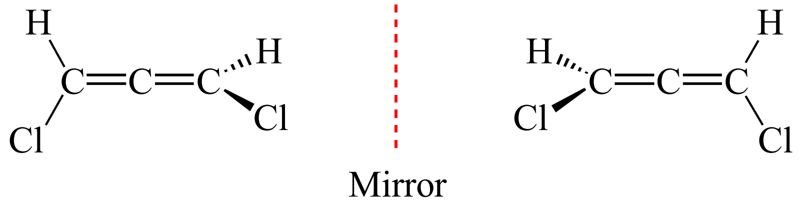
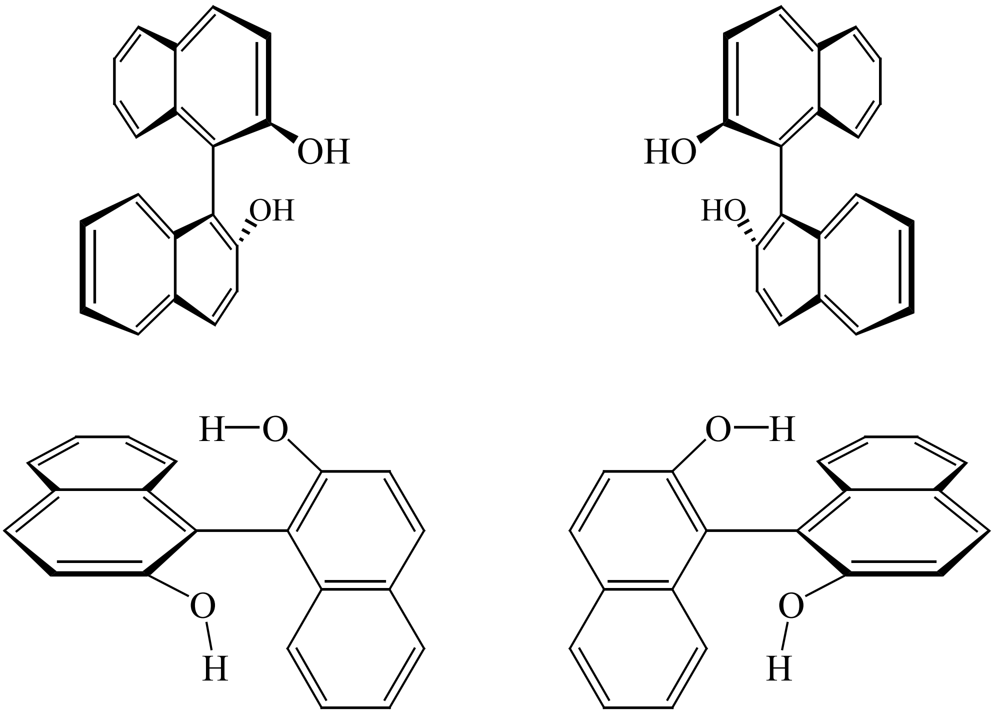


Figure 5.22 Enantiomeric forms of 1,3-dichloroallene. These two molecules are nonsuperposable mirror images of each other and are therefore chiral. They do not possess a tetrahedral atom with four different groups, however.

Binaphthol



IONIC REACTIONS — NUCLEOPHILIC SUBSTITUTION AND ELIMINATION REACTIONS OF ALKYL HALIDES

Breaking Bacterial Cell Walls with Organic Chemistgry

1. Enzymes **catalyze metabolic reactions**, **the flow of genetic information**, **the synthesis of molecules that provide biological structure**, and **help defend us against infections and disease**.
   1) All reactions catalyzed by enzymes occur on the basis of rational chemical reactivity.
   2) The mechanisms utilized by enzymes are essentially those in organic chemistry.

2. **Lysozyme:**
   1) Lysozyme is an enzyme in nasal mucus that fights infection by degrading bacterial cell walls.
   2) Lysozyme generates a carbocation within the molecular architecture of the bacterial cell wall.
      i) Lysozyme stabilizes the carbocation by providing a nearby negatively charged site from its own structure.
      ii) It facilitates cleavage of cell wall, yet does not involve bonding of lysozyme itself with the carbocation intermediate in the cell wall.

6.1 INTRODUCTION

1. **Classes of Organohalogen Compounds (Organohalides):**
   1) **Alkyl halides:** a halogen atom is bonded to an sp^3-hybridized carbon.

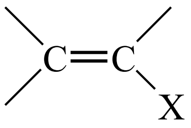
CH_2Cl_2	$CHCl_3$	CH_3I	CF_2Cl_2
dichloromethane **methylene chloride**	**trichloromethane** **chloroform**	**iodomethane** **methyl iodide**	**dichlorodifluoromethane** **Freon-12**

$CCl_3–CH_3$ — **1,1,1-trichloroethane**

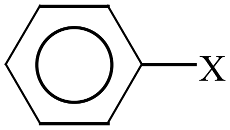
$CF_3–CHClBr$ — **2-bromo-2-chloro-1,1,1-trifluoroethane (Halothane)**

2) **Vinyl halides:** a halogen atom is bonded to an *sp*^{2}-hybridized carbon.

3) **Aryl halides:** a halogen atom is bonded to an *sp*^{2}-hybridized aromatic carbon.



A vinylic halide



A phenyl halide or aryl halide

2. **Importantance of Organohalogen Compounds:**

1) **Solvents:**

i) Alkyl halides are used as **solvents** for **relatively non-polar compounds**.

ii) CCl_4, $CHCl_3$, CCl_3CH_3, CH_2Cl_2, $ClCH_2CH_2Cl$, and *etc*.

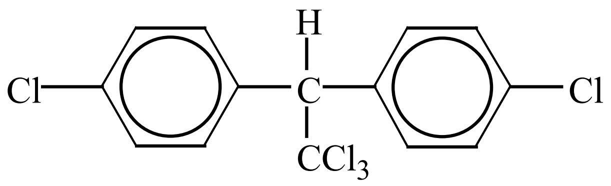
2) **Reagents:**

i) Alkyl halides are used as the **starting materials** for the **synthesis of many compounds**.

ii) Alkyl halides are used in **nucleophilic reactions**, **elimination reactions**, **formation of organometallics**,.and *etc*.

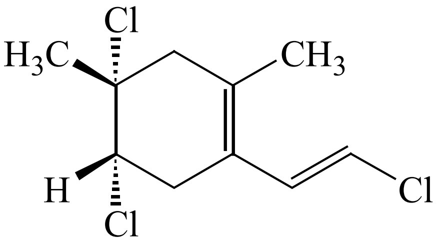
3) **Refrigerants:** Freons (**C**hloro**F**luoro**C**arbon)

4) **Pesticides:** DDT, Aldrin, Chlordan



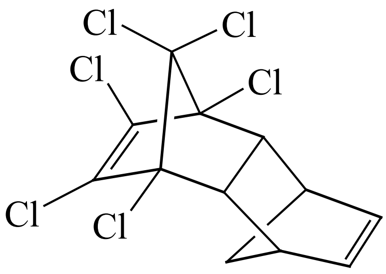
DDT

[1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane]

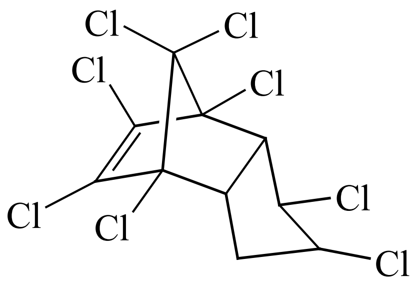


Plocamene B

insecticidal activity against mosquito larvae, similar in activity to DDT



Aldrin

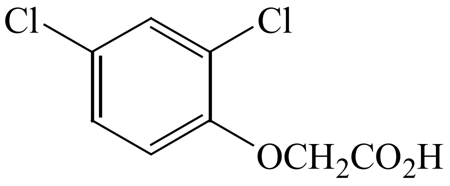


Chlordan

5) **Herbicides:**

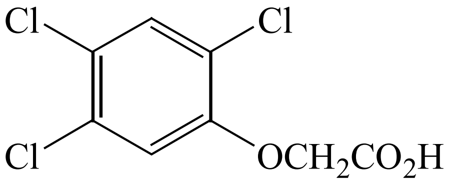
i) Inorganic herbicides are not very selective (kills weeds and crops).

ii) **2,4-D**: Kills broad leaf weeds but allow narrow leaf plants to grow unharmed and in greater yield (0.25 ~ 2.0 lb/acre).



2,4-D

2,4-dichlorophenoxyacetic acid



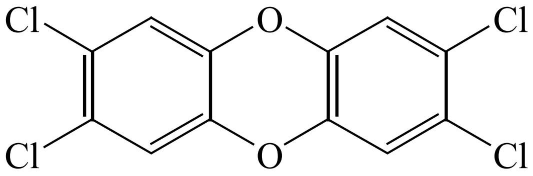
2,4,5-T

2,4,5-trichlorophenoxyacetic acid

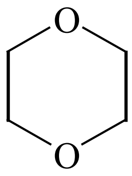
iii) **2,4,5-T**: It is superior to 2,4-D for combating brush and weeds in forest.

iv) **Agent Orange** is a 50:50 mixture of esters of 2,4-D and 2,4,5-T.

v) **Dioxin** is **carcinogenic** (carcinogen — substance that causes cancer), **teratogenic** (teratogen — substance that causes abnormal growth), and **mutagenic** (mutagen — substance that induces hereditary mutations).

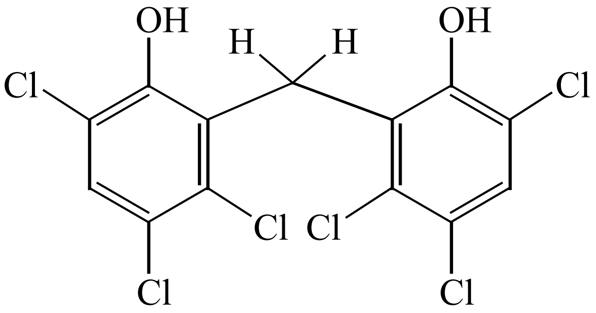


2,3,6,7-tetrachlorodibenzodioxin (TCDD)



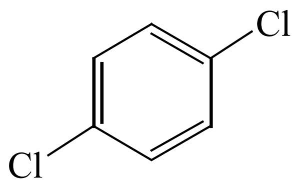
dioxane (1,4-dioxane)

6) **Germicides:**



hexachlorophene

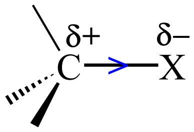
disinfectant for skin



***para*-dichlorobenzene**

used in mothballs

3. **Polarity of C–X bond:**



1) The carbon-halogen bond of alkyl halides is ***polarized***.
2) The **carbon** atom bears a partial **positive** charge, the **halogen** atom a partial **negative** charge.

4. **The bond length of C–X bond:**

Table 6.1 **Carbon-Halogen Bond Lengths, Bond Strength and Dipole Moment**

Bond	Bond Length (Å)	Bond Strength (Kcal/mol)	Dipole Moment (*D*)
CH_3–F	1.39	109	1.82
CH_3–Cl	1.78	84	1.94
CH_3–Br	1.93	70	1.79
CH_3–I	2.14	56	1.64

1) The size of the halogen atom increases going down the periodic table ⇒ the C–X bond length increases going down the periodic table.

6.2 PHYSICAL PROPERTIES OF ORGANIC HALIDES

Table 6.2 Organic Halides

Group	Fluoride		Chloride		Bromide		Iodide	
	bp (°C)	Density (g mL^{-1})	bp (°C)	Density (g mL^{-1})	bp (°C)	Density (g mL^{-1})	bp (°C)	Density (g mL^{-1})
Methyl	–78.4	0.84^{-60}	–23.8	0.92^{20}	3.6	1.73^{0}	42.5	2.28^{20}
Ethyl	–37.7	0.72^{20}	13.1	0.91^{15}	38.4	1.46^{20}	72	1.95^{20}
Propyl	–2.5	0.78^{-3}	46.6	0.89^{20}	70.8	1.35^{20}	102	1.74^{20}
Isopropyl	–9.4	0.72^{20}	34	0.86^{20}	59.4	1.31^{20}	89.4	1.70^{20}
Butyl	32	0.78^{20}	78.4	0.89^{20}	101	1.27^{20}	130	1.61^{20}
sec-Butyl			68	0.87^{20}	91.2	1.26^{20}	120	1.60^{20}
Isobutyl			69	0.87^{20}	91	1.26^{20}	119	1.60^{20}
tert-Butyl	12	0.75^{12}	51	0.84^{20}	73.3	1.22^{20}	100 dec[a]	1.57^{0}
Pentyl	62	0.79^{20}	108.2	0.88^{20}	129.6	1.22^{20}	155^{740}	1.52^{20}
Neopentyl			84.4	0.87^{20}	105	1.20^{20}	127 dec[a]	1.53^{13}
CH_2=CH–	–72	0.68^{26}	–13.9	0.91^{20}	16	1.52^{14}	56	2.04^{20}
CH_2=$CHCH_2$–	–3		45	0.94^{20}	70	1.40^{20}	102-103	1.84^{22}
C_6H_5–	85	1.02^{20}	132	1.10^{20}	155	1.52^{20}	189	1.82^{20}
$C_6H_5CH_2$–	140	1.02^{25}	179	1.10^{25}	201	1.44^{22}	93^{10}	1.73^{25}

[a] Decomposes is abbreviated dec.

1. **Solubilities:**
   1) Many alkyl and aryl halides have very low solubilities in water, but they are miscible with each other and with other relatively nonpolar solvents.
   2) Dichloromethane (CH_2Cl_2, ***methylene chloride***), trichloromethane ($CHCl_3$, ***chloroform***), and tetrachloromethane (CCl_4, ***carbon tetrachloride***) are often used as solvents for nonpolar and moderately polar compounds.

2. Many chloroalkanes, including $CHCl_3$ and CCl_4, have a **cumulative toxicity** and are **carcinogenic**.

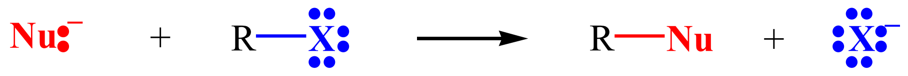
3. **Boiling points:**
   1) Methyl iodide (bp 42 °C) is the only monohalomethane that is a liquid at room

temperature and 1 atm pressure.

2) Ethyl bromide (bp 38 °C) and ethyl iodide (bp 72 °C) are both liquids, but ethyl chloride (bp 13 °C) is a gas.
3) The propyl chlorides, propyl bromides, and propyl iodides are all liquids.
4) In general, higher alkyl chlorides, bromides, and iodides are all liquids and tend to have boiling points near those of alkanes of similar molecular weights.
5) **Polyfluoroalkanes** tend to have **unusually low boiling points**.
   i) Hexafluoroethane boils at –79 °C, even though its molecular weight (MW = 138) is near that of decane (MW = 144; bp 174 °C).

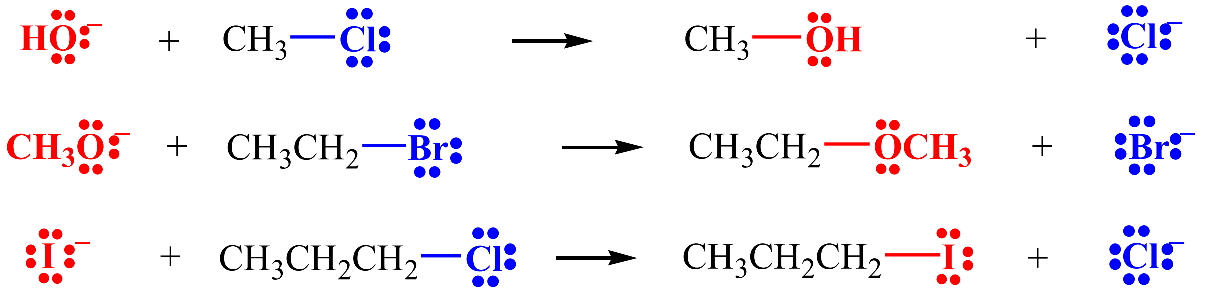
6.3 NUCLEOPHILIC SUBSTITUTION REACTIONS

1. **Nucleophilic Substitution Reactions:**



Nucleophile **Alkyl halide (substrate)** **Product** **Halide ion**

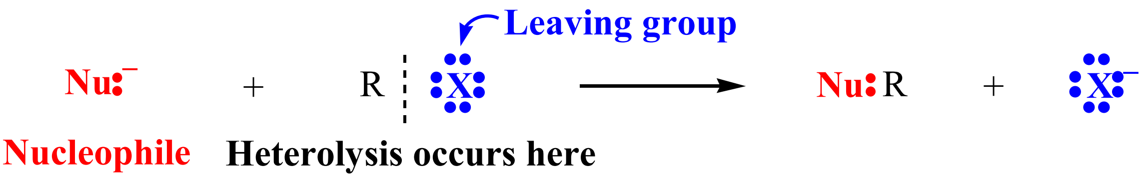
***Examples*:**



2. A **nucleophile**, a species with an **unshared electron pair** (**lone-pair electrons**), reacts with an **alkyl halide** (**substrate**) by replacing the halogen substituent (**leaving group**).

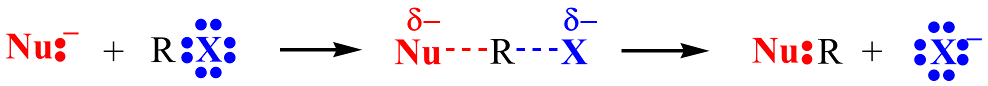
3. In nucleophilic substitution reactions, the C–X bond of the substrate undergoes ***heterolysis***, and the lone-pair electrons of the nucleophile is used to form a new

bond to the carbon atom:

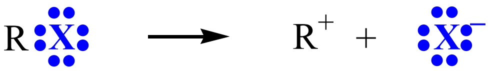


4. **When does the C–X bond break?**

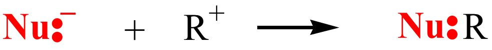
1) Does it break at the same time that the new bond between the nucleophile and the carbon forms?



2) Does the C–X bond break first?



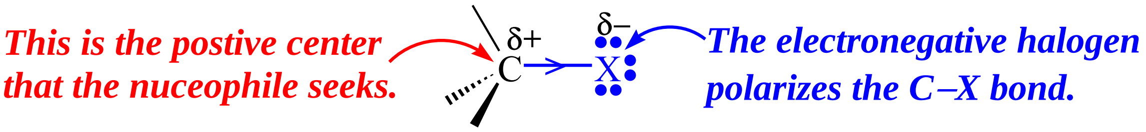
And then



6.4 NUCLEOPHILES

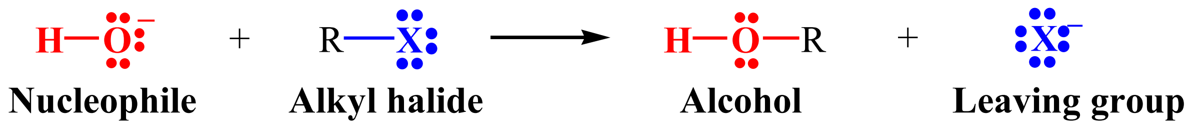
1. A **nucleophile** is a reagent that seeks **positive center**.

1) The word nucleophile comes from ***nucleus***, the positive part of an atom, plus -***phile*** from Greek word ***philos*** meaning to **love**.

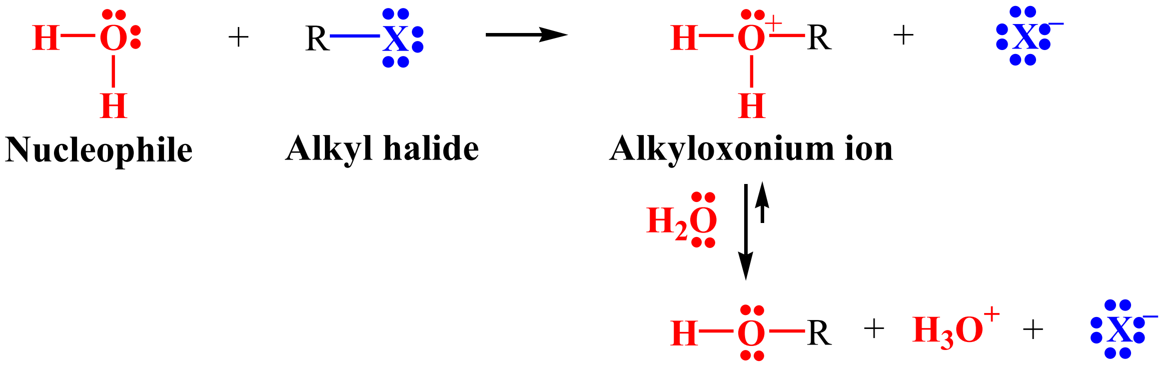


2. A **nucleophile** is any **negative ion** or any **neutral molecule** that has at least **one unshared electron pair**.

1) ***General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion***



2) ***General Reaction for Nucleophilic Substitution of an Alkyl Halide by Water***



i) The first product is an alkyloxonium ion (protonated alcohol) which then loses a proton to a water molecule to form an alcohol.

6.5 Leaving Groups

1. ***To be a good leaving group the substituent must be able to leave as a relatively stable, weakly basic molecule or ion.***

1) In alkyl halides the leaving group is the halogen substituent — it leaves as a halide ion.

i) Because halide ions are relatively stable and very weak bases, they are good leaving groups.

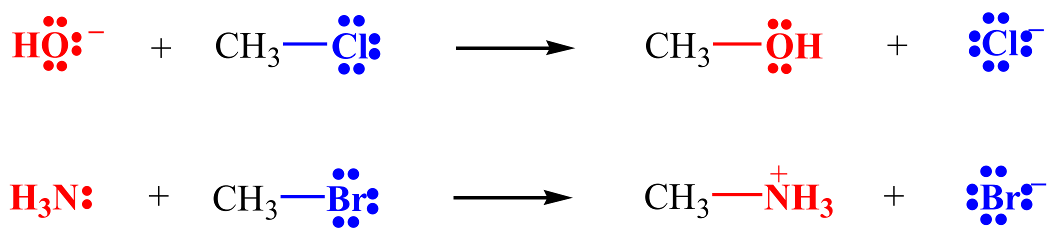
2. ***General equations for nucleophilic substitution reactions:***

$$\mathrm{Nu{:}^-} + \mathrm{R{-}L} \longrightarrow \mathrm{R{-}Nu} + \mathrm{{:}L^-}$$

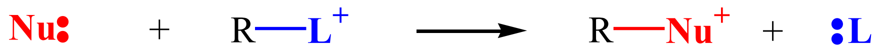
or

$$\mathrm{Nu{:}} + \mathrm{R{-}L} \longrightarrow \mathrm{R{-}Nu^+} + \mathrm{{:}L^-}$$

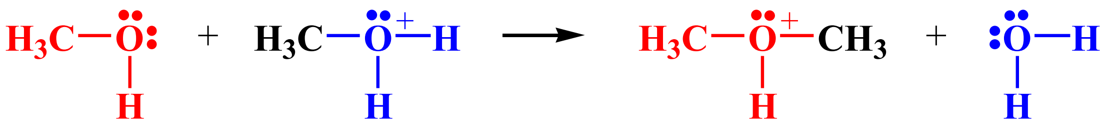
Specific Examples:



3. ***Nucleophilic substitution reactions where the substarte bears a formal positive charge*:**



***Specific Example*:**



6.6 KINETICS OF A NUCLEOPHILIC SUBSTITUTION REACTION: AN S_N2 REACTION

1. **Kinetics:** the relationship between reaction rate and reagent concentration
2. The reaction between methyl chloride and hydroxide ion in aqueous solution:

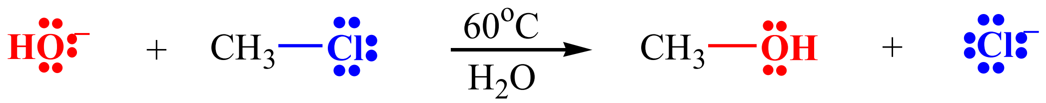


Table 6.3 Rate Study of Reaction of $CHCl_3$ with OH^- at 60 °C

Experimental Number	Initial $[CH_3Cl]$	Initial $[OH^-]$	Initial (mol L^{-1} s^{-1})
1	0.0010	1.0	4.9×10^{-7}
2	0.0020	1.0	9.8×10^{-7}
3	0.0010	2.0	9.8×10^{-7}
4	0.0020	2.0	19.6×10^{-7}

1) The rate of the reaction can be determined experimentally by measuring the rate at which **methyl chloride** or **hydroxide ion** ***disappears*** from the solution, or the

rate at which **methanol** or **chloride ion** ***appears*** in the solution.

2) The ***initial rate*** of the reaction is measured.

2. The rate of the reaction depends on the concentration of **methyl chloride** and the concentration of **hydroxide ion**.

1) **Rate equation:** Rate ∝ $[CH_3Cl] [OH^-]$ ⇒ Rate = $k [CH_3Cl] [OH^-]$

i) k is the rate constant.

2) Rate = $k [A]^a [B]^b$

i) The overall order of a reaction is equal to the sum of the exponents a and b.

ii) For example: Rate = $k [A]^2 [B]$

The reaction is second order with respect to [A], first order wirth respect to [B], and third order overall.

3. **Reaction order:**

1) The reaction is **second order overall**.

2) The reaction is **first order** with respect to **methyl chloride** and **first order** with respect to **hydroxide ion**.

4. For the reaction to take place a **hydroxide ion** and **methyl chloride** molecule **must collide**.

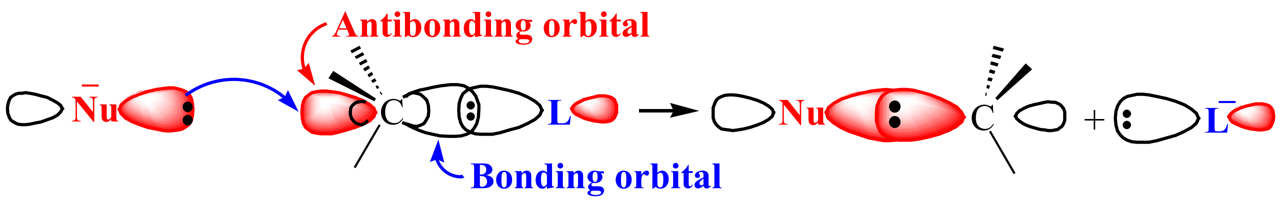
1) The reaction is **bimolecular** — two species are involved in the **rate-determining step**.

3) The **S_N2 reaction: Substitution, Nucleophilic, bimolecular**.

6.7 A MECHANISM FOR THE S_N2 REACTION

1. The **mechanism** for **S_N2 reaction:**

1) Proposed by Edward D. Hughes and Sir Christopher Ingold (the University College, London) in 1937.



2) The **nucleophile** attacks the carbon bearing the **leaving group** from the **back side**.

   i) The orbital that contains the **electron pair** of the **nucleophile** begins to **overlap** with an **empty** (**antibonding**) **orbital** of the carbon bearing the **leaving group**.

   ii) The bond between the **nucleophile** and the carbon atom is **forming**, and the bond between the carbon atom and the **leaving group** is **breaking**.

   iii) The formation of the bond between the **nucleophile** and the carbon atom provides most of the energy necessary to break the bond between the carbon atom and the **leaving group**.

2. **Walden inversion:**

1) The **configuration** of the carbon atom becomes **inverted** during **S_N2** reaction.
2) The first observation of such an inversion was made by the Latvian chemist Paul Walden in 1896.

3. **Transition state:**

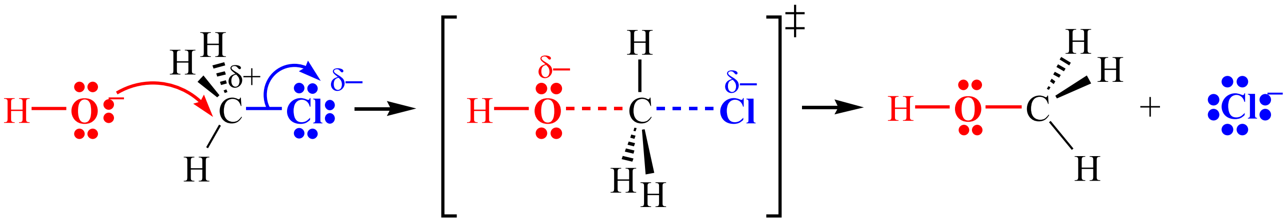
1) The **transition state** is a fleeting arrangement of the atoms in which the nucleophile and the leaving group are both bonded to the carbon atom undergoing attack.
2) Because the **transition state** involves both the nucleophile and the substrate, it accounts for the observed second-order reaction rate.
3) Because bond formation and bond breaking occur simultaneously in a single transition state, the S_N2 reaction is a ***concerted reaction***.
4) Transition state lasts only as long as the time required for one molecular vibration, about 10^{-12} s.

A Mechanism for the S_N2 Reaction

Reaction:

$$HO^- + CH_3Cl \longrightarrow CH_3OH + Cl^-$$

Mechanism:



Transtion state

The negative hydroxide ion pushes a pair of electrons into the partially positive carbon from the back side. The chlorine begins to move away with the pair of electrons that have bonded it to the carbon.

In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon begins to invert.

Now the bond between the oxygen and carbon has formed and the chloride has departed. The configuration of the carbon has inverted.

6.8 TRANSIITION STATE THEORY: FREE-ENERGY DIAGRAMS

1. **Exergonic** and **endergonic**:
   1) A reaction that proceeds with a **negative** **free-energy change** is **exergonic**.
   2) A reaction that proceeds with a **positive** **free-energy change** is **endergonic**.

2. The reaction between CH_3Cl and HO^- in aqueous solution is highly **exergonic**.
   1) At 60 °C (333 K), $\Delta G° = –100$ kJ mol^{-1} (–23.9 Kcal mol^{-1}).
   2) The reaction is also **exothermic**, $\Delta H° = –75$ kJ mol^{-1}.

$$HO^- + CH_3Cl \longrightarrow CH_3OH + Cl^- \qquad \Delta G° = –100 \text{ kJ mol}^{-1}$$

3. The **equilibrium constant** for the reaction is extremely large:

$$\Delta G^\circ = -2.303\ RT \log K_{eq} \Rightarrow \log K_{eq} = \frac{-\Delta G^\circ}{2.303\ RT}$$

$$\log K_{eq} = \frac{-\Delta G^\circ}{2.303\ RT} = \frac{-(-100\ \text{kJ mol}^{-1})}{2.303 \times 0.00831\ \text{kJ K}^{-1}\ \text{mol}^{-1} \times 333\ \text{K}} = 15.7$$

$$K_{eq} = 5.0 \times 10^{15}$$

$$\text{R} = 0.08206\ \text{L atm mol}^{-1}\ \text{K}^{-1} = 8.3143\ \text{j mol}^{-1}\ \text{K}^{-1}$$

1) A reaction goes to **completion** with such a large equilibrium constant.
2) The energy of the reaction goes **downhill**.

4. If **covalent bonds are broken** in a reaction, the **reactants must go up an energy hill first**, before they can go downhill.

1) **A free-energy diagram:** a plotting of the **free energy** of the reacting particles against the **reaction coordinate**.

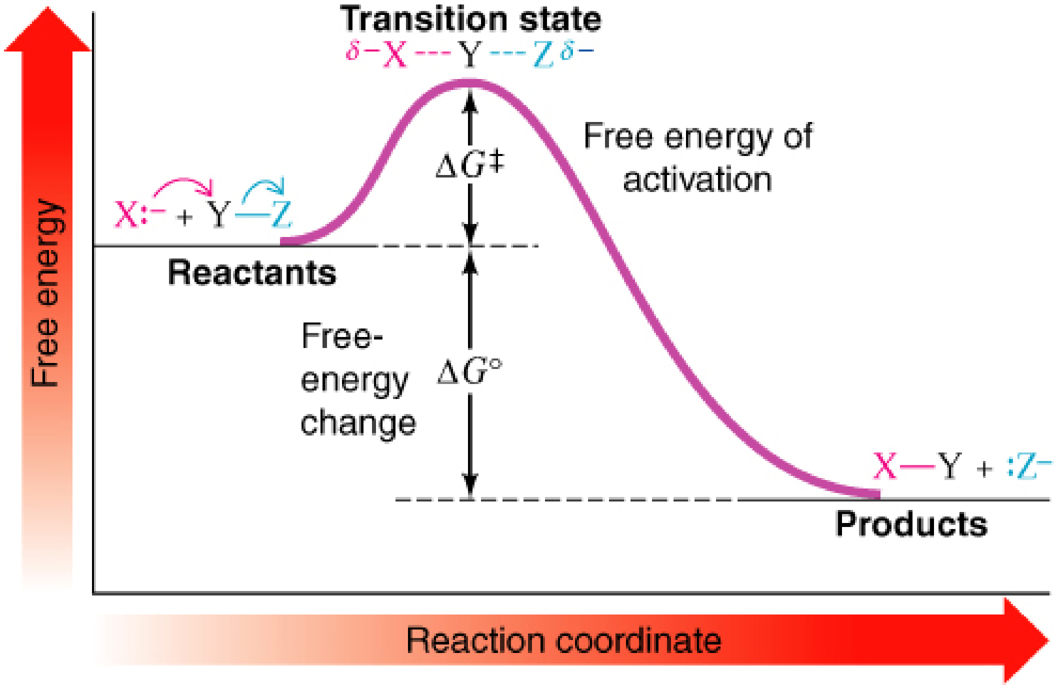


Figure 6.1 **A free-energy diagram for a hypothetical S_N2 reaction that takes place with a negative ΔG°.**

2) The reaction coordinate measures the progress of the reaction. It represents the

changes in bond orders and bond distances that must take place as the reactants are converted to products.

5. **Free energy of activation, $\Delta G^{\ddagger}$:**

1) The height of the **energy barrier** between the reactants and products is called the **free energy of activation**.

6. **Transition state:**

1) The top of the energy hill corresponds to the transition state.
2) *The difference in free energy between the reactants and the transition state is the* ***free energy of activation***, $\Delta G^{\ddagger}$.
3) *The difference in free energy between the reactants and the products is the* ***free energy change*** *for the reaction*, $\Delta G°$.

7. A free-energy diagram for an endergonic reaction:

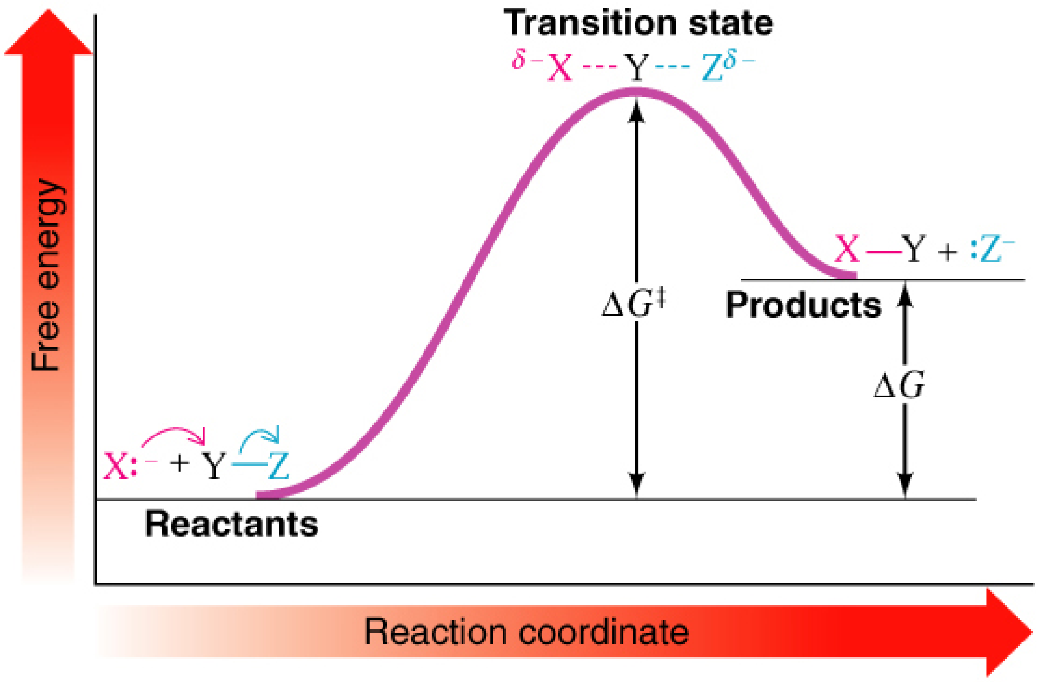


Figure 6.2 **A free-energy diagram for a hypothetical reaction with a positive free-energy change.**

1) The energy of the reaction goes **uphill**.
2) $\Delta G^{\ddagger}$ will be larger than $\Delta G°$.

8. **Enthalpy of activation** ($\Delta H^{\ddagger}$) and **entropy of activation** ($\Delta S^{\ddagger}$):

$$\Delta G° = \Delta H° – \Delta S° \quad \Rightarrow \quad \Delta G^{\ddagger} = \Delta H^{\ddagger} – \Delta S^{\ddagger}$$

1) $\Delta H^{\ddagger}$ is the difference in bond energies between the reactants and the transition state.
   - i) It is the energy necessary to bring the reactants close together and to bring about the partial breaking of bonds that must happen in the transition state.
   - ii) Some of this energy may be furnished by the bonds that are partially formed.

2) $\Delta S^{\ddagger}$ is the difference in entropy between the reactants and the transition state.
   - i) Most reactions require the reactants to come together with a particular orientation.
   - ii) This requirement for a particular orientation means that the transition state must be more ordered than the reactants and that $\Delta S^{\ddagger}$ will be negative.
   - iii) The more highly ordered the transition state,the more negative $\Delta S^{\ddagger}$ will be.
   - iv) **A three-dimensional plot of free energy versus the reaction coordinate:**

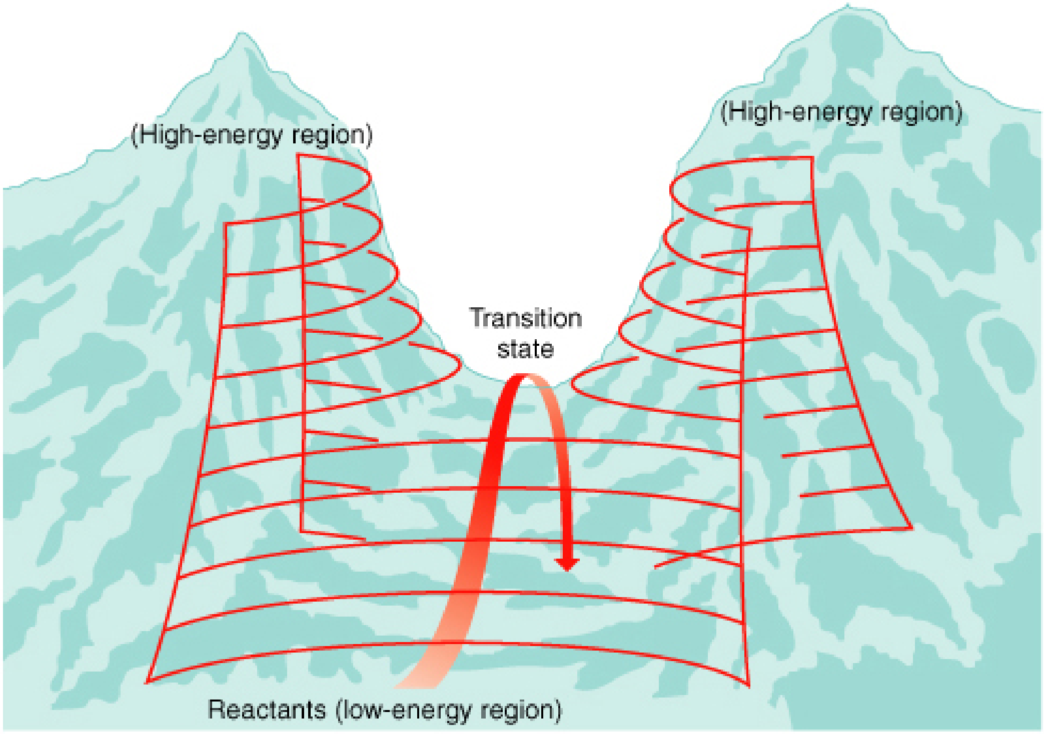


Figure 6.3 **Mountain pass or col analogy for the transition state.**

v) The transition state resembles a mountain pass rather than the top of an energy hill.

vi) The reactants and products appear to be separated by an energy barrier resembling a mountain range.

vii) Transition state lies at the top of the route that requires the lowest energy climb. Whether the pass is a wide or narrow one depends on $\Delta S^{\ddagger}$.

viii) A wide pass means that there is a relatively large number of orientations of reactants that allow a reaction to take place.

9. Reaction rate versus temperature:

1) Most chemical reactions occur much more rapidly at higher temperatures ⇒ For many **reactions taking place near room temperature, a *10 °C increase* in temperature will cause the reaction rate to *double***.

i) This dramatic increase in reaction rate results from a large increase in the number of collisions between reactants that together have sufficient energy to surmont the barrier ($\Delta G^{\ddagger}$) at higher temperature.

2) Maxwell-Boltzmann speed distribution:

i) The average **kinetic energy** of gas particles depends on the absolute temperature.

$$KE_{av} = 3/2\ kT$$

k: Boltzmann's constant = $R/N_0 = 1.38 \times 10^{-23}$ J K^{-1}

R = universal gas constant

N_0 = Avogadro's number

ii) In a sample of gas, there is a distribution of velocities, and hence there is a distribution of **kinetic energies**.

iii) As the temperature is increased, the average velocity (and kinetic energy) of the collection of particles increases.

iv) The kinetic energies of molecules at a given temperature are not all the same ⇒ **Maxwell-Boltzmann speed distribution:**

$$F(v) = 4\pi \left(\frac{m}{2\pi k_B T}\right)^{3/2} v^2 e^{-mv^2/2k_B T} = 4\pi (m/2\pi k_B T)^{3/2} v^2 \exp(-mv^2/2k_B T)$$

k: Boltzmann's constant = $R/N_0 = 1.38 \times 10^{-23}$ J K^{-1}

e is 2.718, the base of natural logarithms

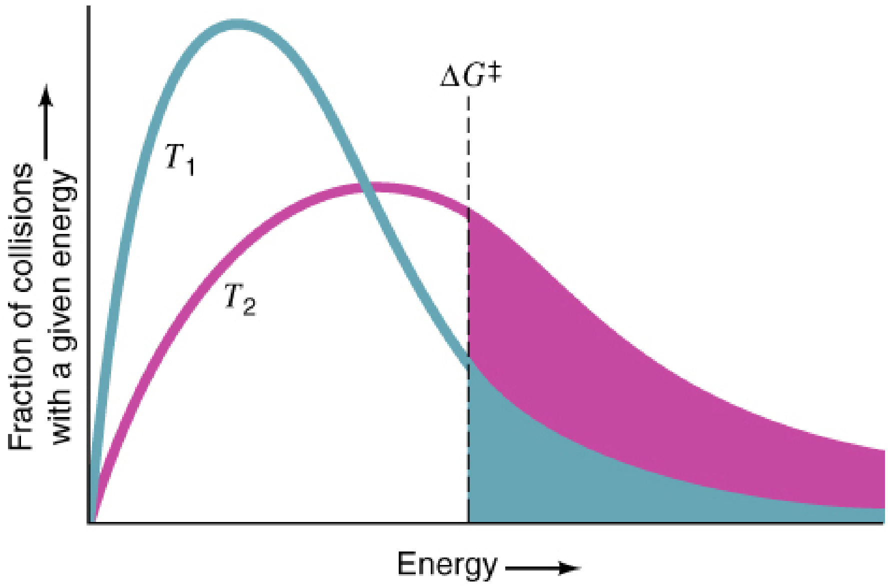


Figure 6.4 **The distribution of energies at two temperatures, T_1 and T_2 ($T_1 > T_2$). The number of collisions with energies greater than the free energy of activation is indicated by the appropriately shaded area under each curve.**

3) Because of the way energies are distributed at different temperature, increasing the temperature by only a small amount causes a large increase in the number of collisions with larger energies.

10. The relationship between the rate constant (k) and $\Delta G^\ddagger$:

$$k = k_0 \ e^{-\Delta G^\ddagger / RT}$$

1) k_0 is the absolute rate constant, which equals the rate at which all transition states proceed to products. At 25 °C, $k_0 = 6.2 \times 10^{12}$ s^{-1}.

2) **A reaction with a lower free energy of activation will occur very much faster than a reaction with a higher one**.

11. If a reaction has a $\Delta G^\ddagger$ less than 84 kJ mol^{-1} (20 kcal mol^{-1}), it will take place readily at room temperature or below. If $\Delta G^\ddagger$ is greater than 84 kJ mol^{-1}, heating

will be required to cause the reaction to occur at a reasonable rate.

12. A free-energy diagram for the reaction of methyl chloride with hydroxide ion:

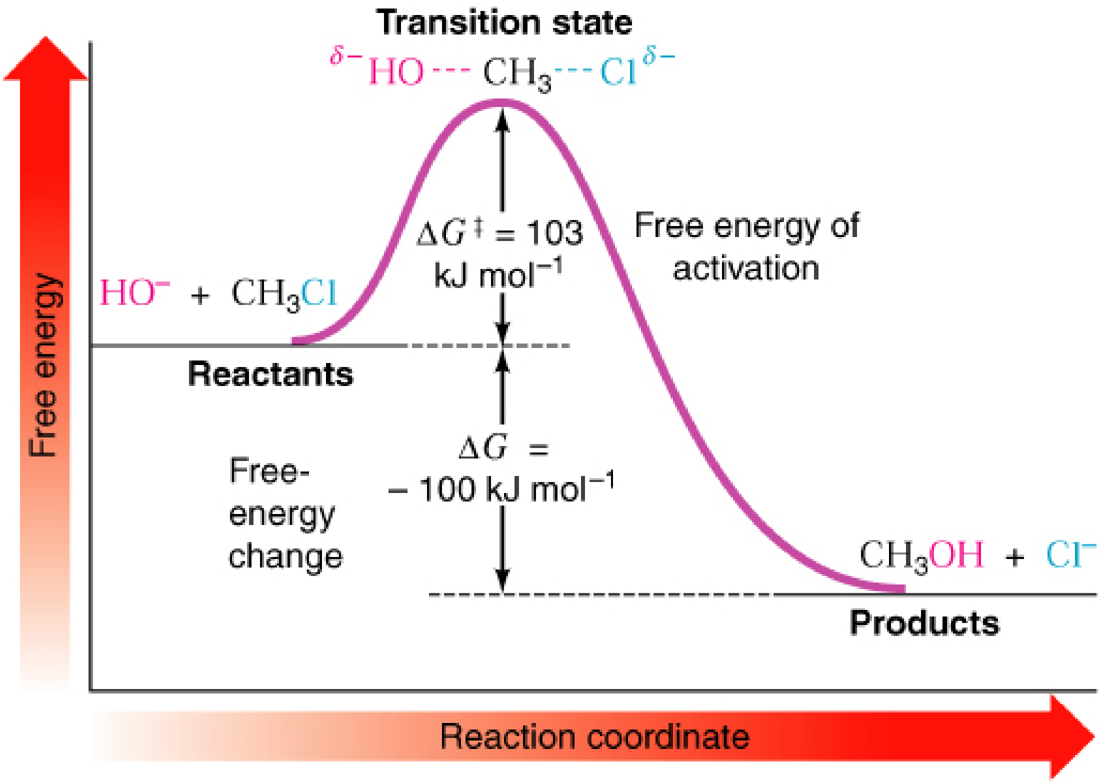


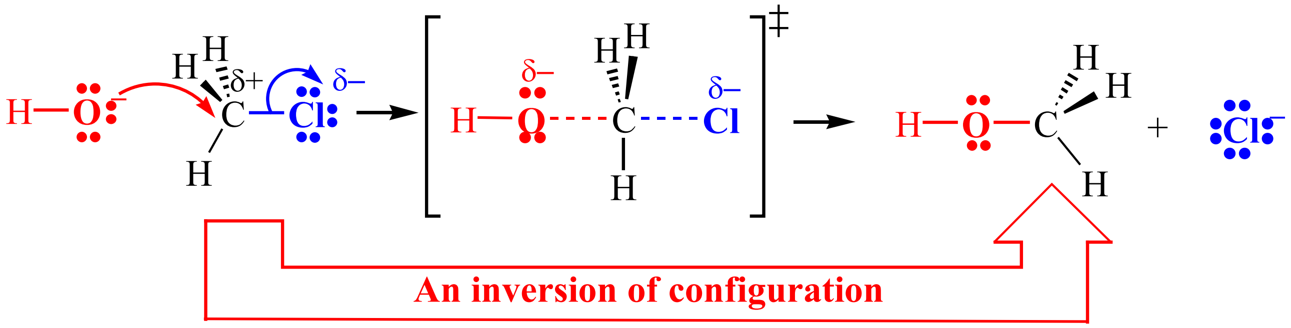
Figure 6.5 **A free-energy diagram for the reaction of methyl chloride with hydroxide ion at 60 °C.**

1) At 60 °C, $\Delta G^{\ddagger}$ = 103 kJ mol^{-1} (24.6 kcal mol^{-1}) ⇒ the reaction reaches completion in a matter of a few hours at this temperature.

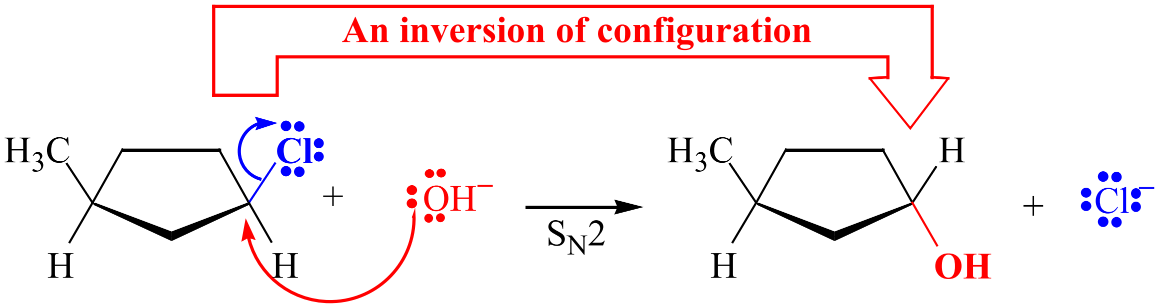
6.9 THE STEREOCHEMISTRY OF S_N2 REACTIONS

1. In an S_N2 reaction, **the nucleophile attacks from the back side**, that is, **from the side directly opposite the leaving group**.

   1) This attack causes **a change in the configuration** (**inversion of configuration**) of the carbon atom that is the target of nucleophilic attack.

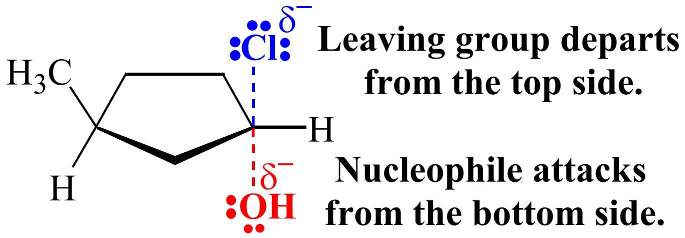


2. **Inversion of configuration** can be observed when hydroxide ion reacts with *cis*-1-chloro-3-methylcyclopentane in an S_N2 reaction:



***cis*-1-Chloro-3-methylcyclopentane** ***trans*-3-methylcyclopentanol**

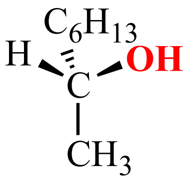
1) The transition state is likely to be:



3. **Inversion of configuration** can be also observed when the S_N2 reaction takes place at a **stereocenter** (with ***complete*** inversion of stereochemistry at the chiral carbon center):

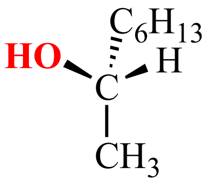
(*R*)-(–)-2-Bromooctane $[\alpha]_D^{25}$ = **–34.25°**

(*S*)-(+)-2-Bromooctane $[\alpha]_D^{25}$ = **+34.25°**



(*R*)-(–)-2-Octanol

$[\alpha]_D^{25}$ = –9.90°



(*S*)-(+)-2-Octanol

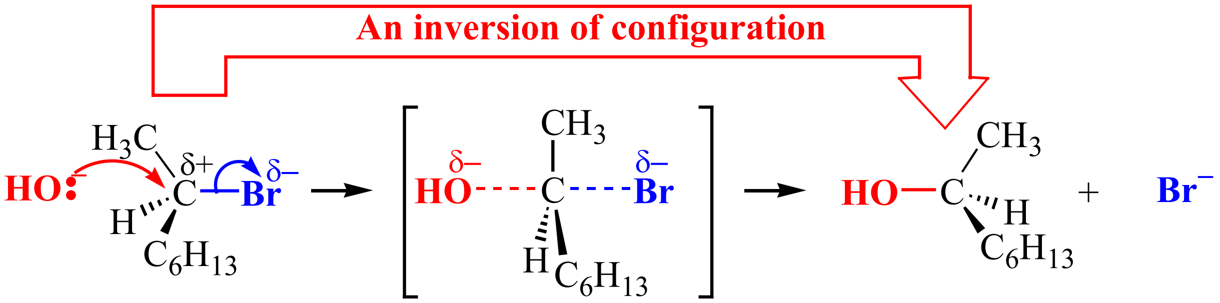
$[\alpha]_D^{25}$ = +9.90°

1) The (*R*)-(–)-2-bromooctane reacts with sodium hydroxide to afford only (*S*)-(+)-2-octanol.

2) **S_N2 reactions always lead to inversion of configuration.**

The Stereochemistry of an S_N2 Reaction

S_N2 Reaction takes place with complete inversion of configuration:



(*R*)-(–)-2-Bromooctane

$[\alpha]_D^{25}$ = –34.25°

Enantiomeric purity = 100%

(*S*)-(+)-2-Octanol

$[\alpha]_D^{25}$ = +9.90°

Enantiomeric purity = 100%

6.10 The Reaction of *tert*-Butyl Chloride with Hydroxide Ion: An S_N1 Reaction

1. When *tert*-butyl chloride with sodium hydroxide in a mixture of water and acetone, the rate of formation of *tert*-butyl alcohol is dependent on the concentration of *tert*-butyl chloride, but is ***independent of the concentration of hydroxide ion***.

1) *tert*-Butyl chloride reacts by substitution at virtually the **same rate** in **pure water** (where the hydroxide ion is 10^{-7} *M*) as it does in **0.05 *M* aqueous sodium hydroxide** (where the hydroxide ion concentration is **500,000 times larger**).

2) The rate equation for this substitution reaction is **first order respect to *tert*-butyl chloride** and ***first order overall***.

$$(CH_3)_3C{-}Cl \quad + \quad OH^- \quad \xrightarrow[H_2O]{\text{acetone}} \quad (CH_3)_3C{-}OH \quad + \quad Cl^-$$

$$\text{Rate} \propto [(CH_3)_3CCl] \quad \Rightarrow \quad \text{Rate} = k\,[(CH_3)_3CCl]$$

2. ***Hydroxide ions*** do not participate in the transition state of the step that controls the rate of the reaction.

1) The reaction is **unimolecular** ⇒ **S_N1** reaction (**Substitution**, **Nucleophilic**, **Unimolecular**).

6.10A MULTISTEP REACTIONS AND THE RATE-DETERMINING STEP

1. The **rate-determining step** or the **rate-limiting step** of a multistep reaction:

Step 1 Reactant $\xrightarrow{\text{slow}}$ Intermediate 1 ⇒ Rate = k_1 [reactant]

Step 2 Intermediate 1 $\xrightarrow{\text{fast}}$ Intermediate 2 ⇒ Rate = k_2 [intermediate 1]

Step 3 Intermediate 2 $\xrightarrow{\text{fast}}$ Product ⇒ Rate = k_3 [intermediate 2]

$$k_1 << k_2 \text{ or } k_3$$

1) The concentration of the intermediates are always very small because of the slowness of step 1, and steps 2 and 3 actuallu occur at the same rate as step 1.

2) Step 1 is the **rate-determining step**.

6.11 A MECHANISM FOR THE S_N1 REACTION

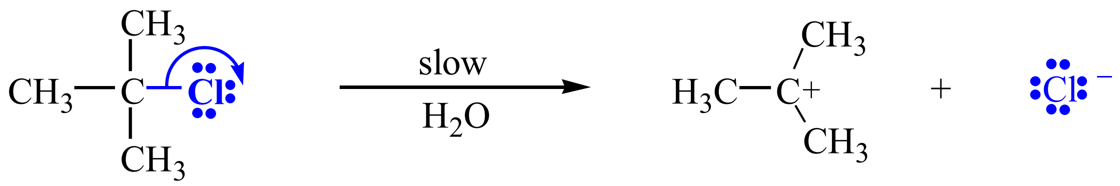
A Mechanism for the S_N1 Reaction

Reaction:

$$(CH_3)_3CCl + 2\ H_2O \xrightarrow{\text{acetone}} (CH_3)_3COH + H_3O^+ + Cl^-$$

Mechanism:

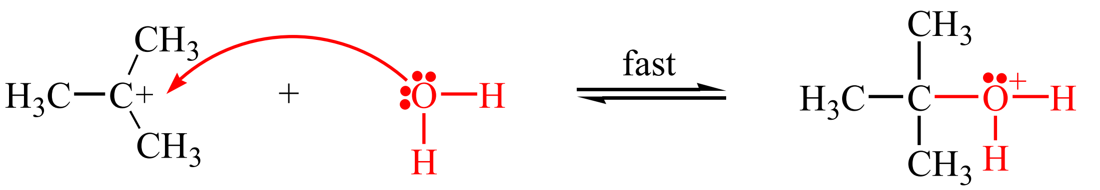
Step 1



Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. Although not shown here, the ions are slovated (and stabilized) by water molecules.

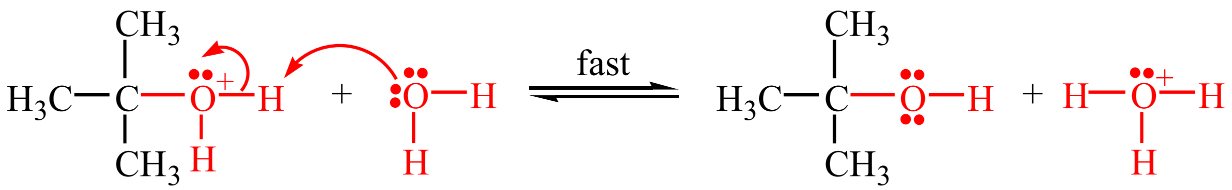
Step 2



A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).

Step 3



A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

The products are *tert*-butyl alcohol and a hydronium ion.

1. The first step is **highly endothermic** and has **high free energy of activation**.

   1) It involves heterolytic cleavage of the C–Cl bond and there is no other bonds are formed in this step.

   2) The free energy of activation is about 630 kJ mol^{-1} (150.6 kcal mol^{-1}) in the gas phase; the free energy of activation is much lower in aqueous solution — about 84 kJ mol^{-1} (20 kcal mol^{-1}).

2. A free-energy diagram for the S_N1 reaction of *tert*-butyl chloride with water:

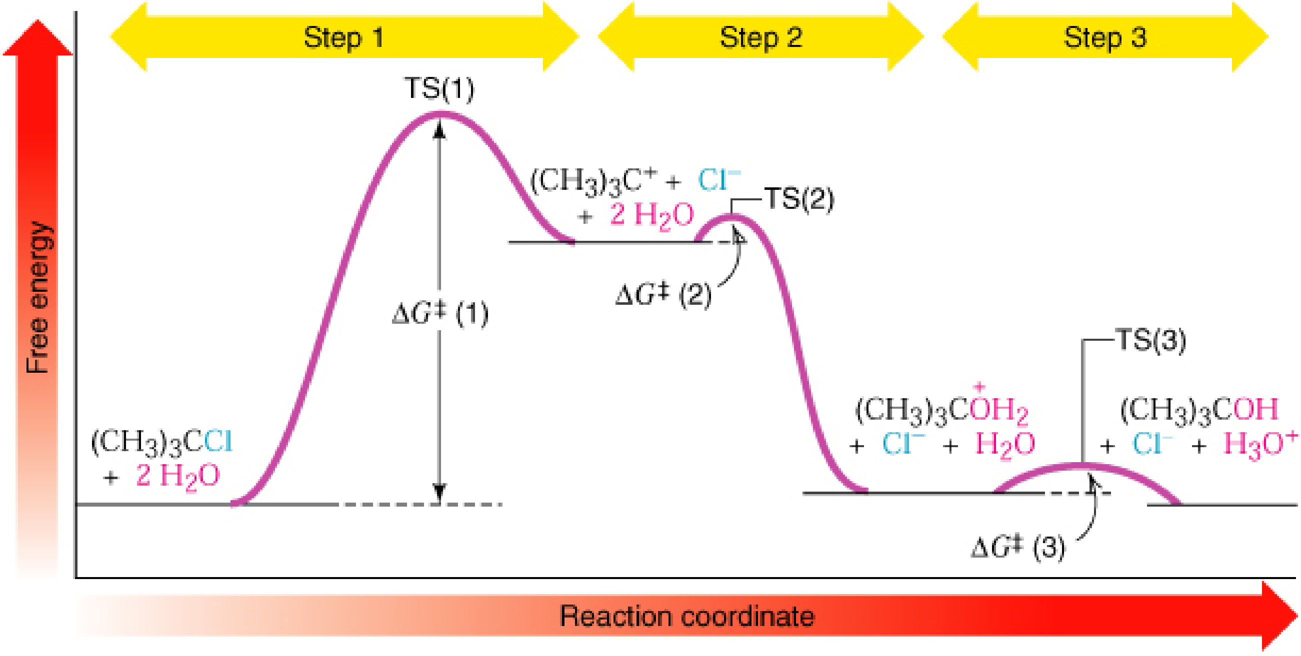
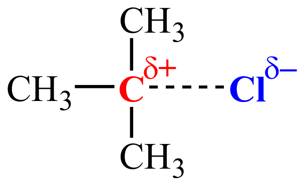


Figure 6.7 **A free-energy diagram for the S_N1 reaction of *tert*-butyl chloride with water. The free energy of activation for the first step, $\Delta G^{\ddagger}(1)$, is much larger than $\Delta G^{\ddagger}(2)$ or $\Delta G^{\ddagger}(3)$. TS(1) represents transition state (1), and so on.**

3. The C–Cl bond of *tert*-butyl chloride is largely broken and ions are beginning to develop in the transition state of the rate-determining step:



6.12 Carbocations

1. In 1962, George A. Olah (Nobel Laureate in chemistry in 1994; now at the University of Southern California) and co-workers published the first of a series of papers describing experiments in which alkyl cations were prepared in an environment in which they were reasonably stable and in which they could be observed by a number of spectroscopic techniques.

6.12A The Structure of Carbocations

1. The structure of **carbocations** is **trigonal planar**.

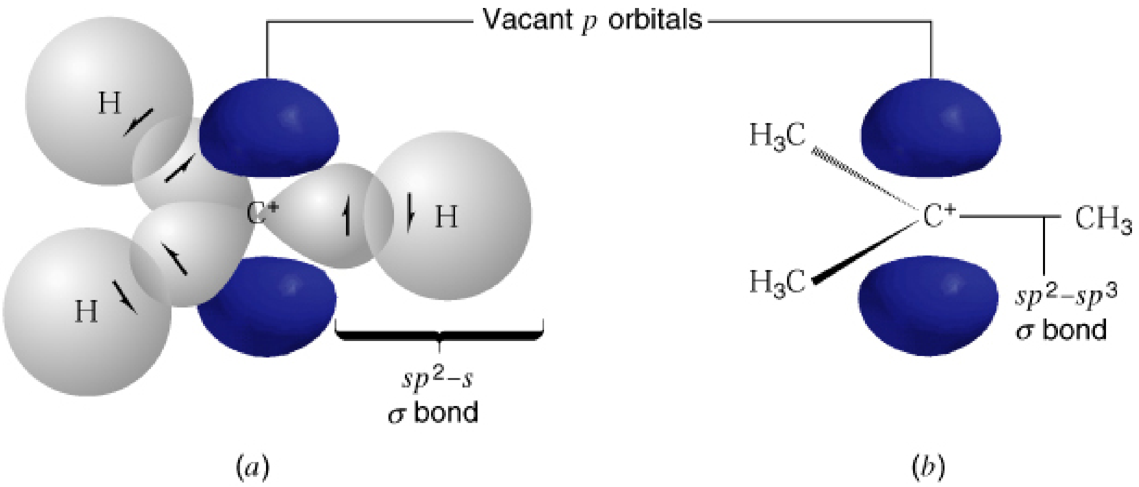
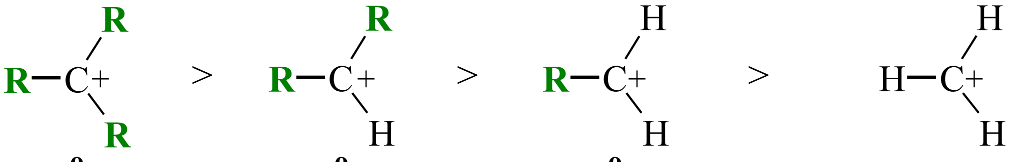


Figure 6.8 **(a) A stylized orbital structure of the methyl cation. The bonds are sigma (σ) bonds formed by overlap of the carbon atom's three sp^2 orbitals with 1s orbitals of the hydrogen atoms. The *p* orbital is vacant. (b) A dashed line-wedge representation of the *tert*-butyl cation. The bonds between carbon atoms are formed by overlap of sp^3 orbitals of the methyl group with sp^2 orbitals of the central carbon atom.**

6.12B The Relative Stabilities of Carbocations

1. **The order of stabilities of carbocations:**



3° > 2° > 1° > Methyl

(most stable) (least stable)

1) **A charged system is stabilized when the charge is dispersed or delocalized**.

2) **Alkyl groups**, when compared to **hydrogen atoms**, are **electron releasing**.

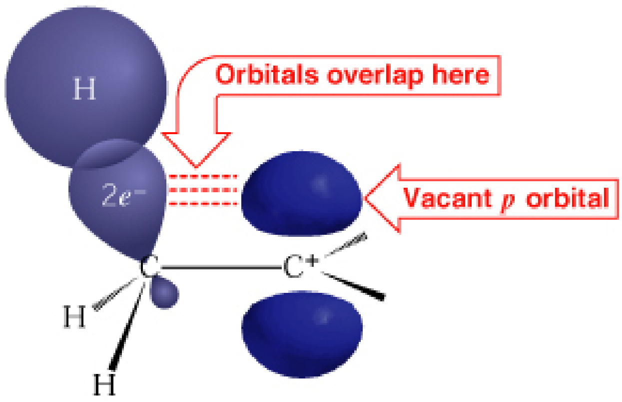
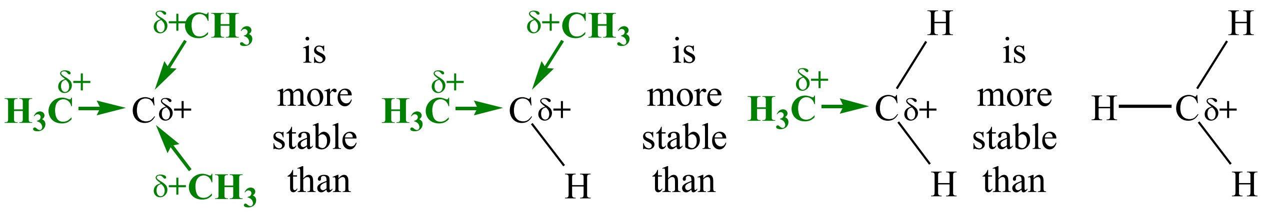


Figure 6.9 ***How a methyl group helps stabilize the positive charge of a carbocation.*** **Electron density from one of the carbon-hydrogen sigma bonds of the methyl group flows into the vacant *p* orbital of the carbocation because the orbitals can partly overlap. Shifting electron density in this way makes the sp^2-hybridized carbon of the carbocation somewhat less positive, and the hydrogens of the methyl group assume some of the positive charge. Delocalization (dispersal) of the charge in this way leads to greater stability. This interaction of a bond orbital with a *p* orbital is called hyperconjugation.**

2. **The delocalization of charge and the order of stability of carbocations parallel the number of attached methyl groups.**



***tert*-Butyl cation (3°) (most stable)** | **Isopropyl cation (2°)** | **Ethyl cation (1°)** | **Methyl cation (least stable)**

3. **The relative stabilities of carbocations is 3° > 2° > 1° > methyl**.

4. **The electrostatic potential maps for carbocations:**

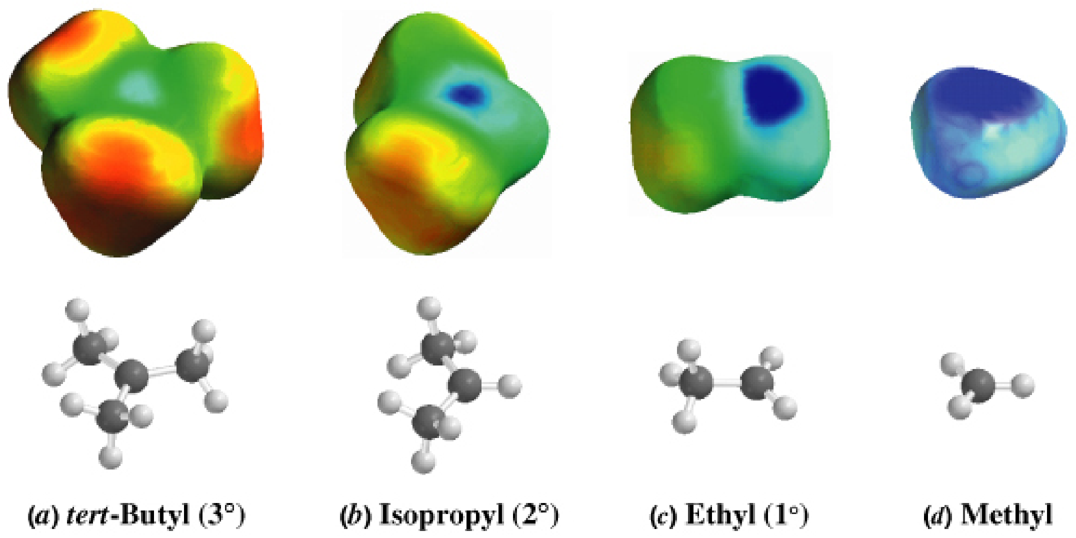
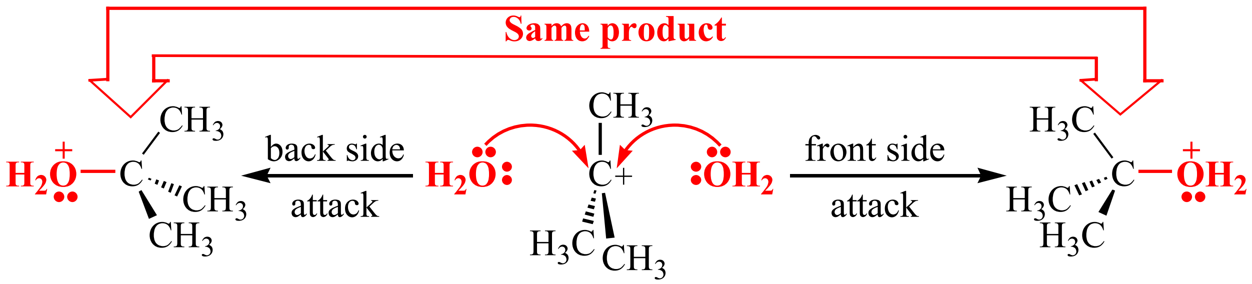


Figure 6.10 **Electrostatic potential maps for (a) *tert*-butyl (3°), (b) isopropyl (2°), (c) ethyl (1°), and (d) methyl carbocations show the trend from greater to lesser delocalization (stabilization) of the positive charge. (The structures are mapped on the same scale of electrostatic potential to allow direct comparison.)**

6.13 THE STEREOCHEMISTRY OF S_N1 REACTIONS

1. The carbocation has a **trigonal planar structure** ⇒ It may react with a **nucleophile** from either the **front side** or the **back side**:



   1) With the *tert*-butyl cation it makes no difference.
   2) With some cations, **different products** arise from the two reaction possibilities.

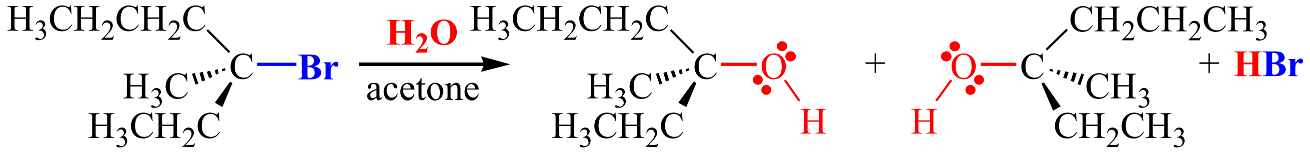
6.13A REACTIONS THAT INVOLVE RACEMIZATION

1. **Racemization:** a reaction that transforms an optically active compound into a racemic form.

1) **Complete racemization** and **partial racemization:**

2) **Racemization** takes place **whenever the reaction causes chiral molecules to be converted to an achiral intermediate**.

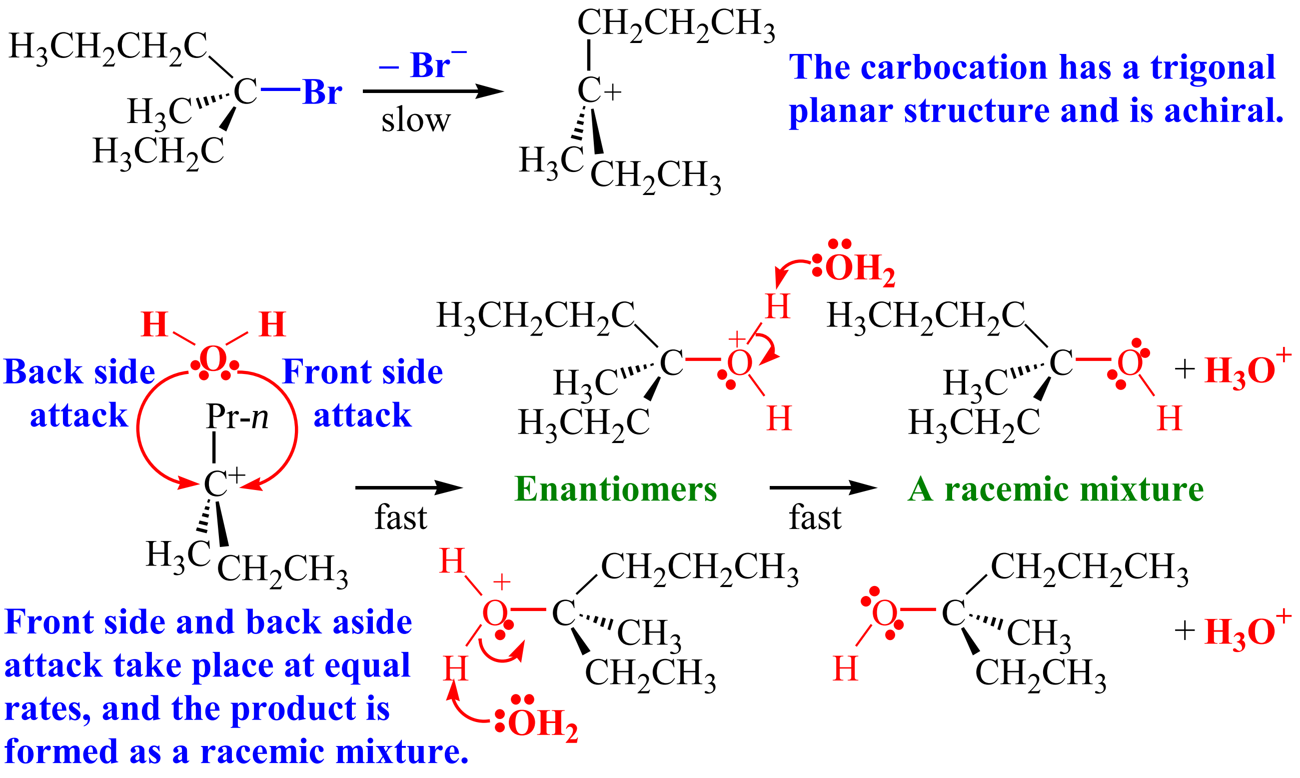
2. Heating optically active (*S*)-3-bromo-3-methylhexane with aqueous acetone results in the formation of racemic 3-methyl-3-hexanol.



(*S*)-3-bromo-3-methylhexane (optically active) **(*S*)-3-methyl-3-hexanol** **(*R*)-3-methyl-3-hexanol (optically inactive, a racemic form)**

i) The S_N1 reaction proceeds through the formation of an ***achiral*** trigonal planar carbocation intemediate.

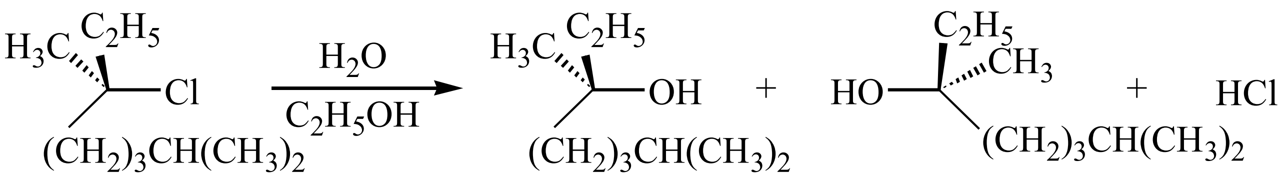
The stereochemistry of an S_N1 Reaction



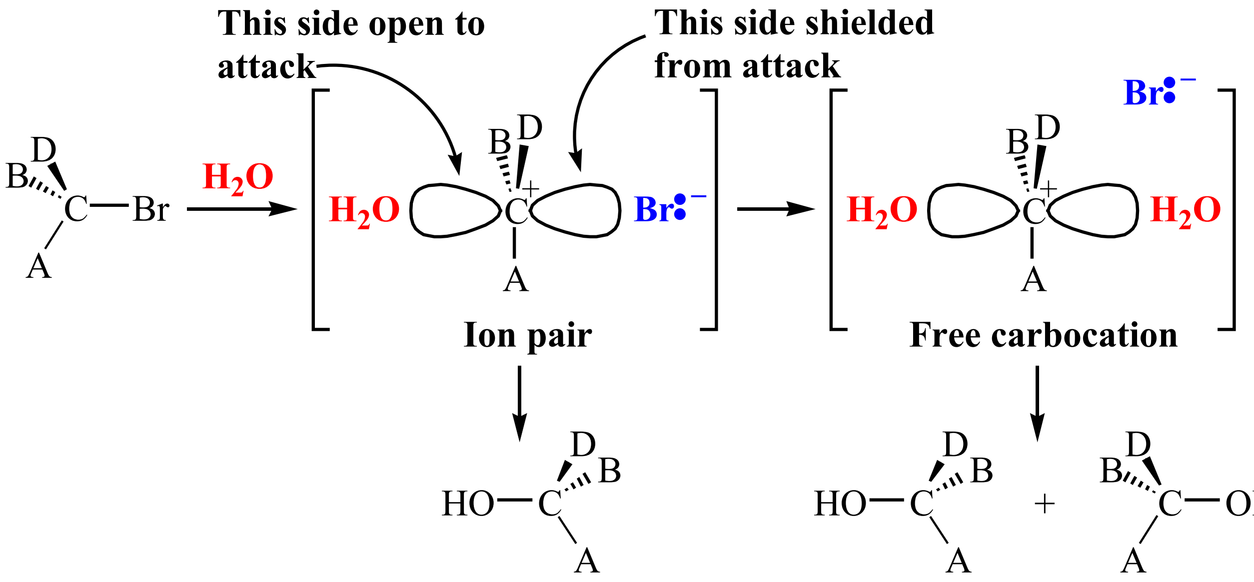
The S_N1 reaction of (*S*)-3-bromo-3-methylhexane proceeds with racemization because the intermediate carbocation is achiral and attacked by the nucleophile can occur from either side.

3. **Few S_N1 displacements occur with complete racemization**. Most give a minor

(0 ~ 20 %) amount of inversion.



(*R*)-6-Chloro-2,6-dimethyloctane | **40% *R* (retention)** | **60% *S* (inversion)**



Inversion | **Racemization**

6.13B Solvolysis

1. **Solvolysis** is a nucleophilic substitution in which **the nucleophile is a molecule of the solvent** (**solvent + *lysis***: cleavage by the solvent).
   1) **Hydrolysis**: when the solvent is water.
   2) **Alcoholysis**: when the solvent is an alcohol (e.g. **methanolysis**).

Examples of Solvolysis

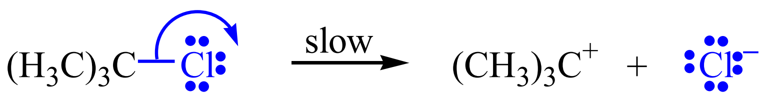
$$(H_3C)_3C{-}Br \quad + \quad H_2O \longrightarrow (H_3C)_3C{-}OH \quad + \quad HBr$$

$$(H_3C)_3C{-}Cl \quad + \quad CH_3OH \longrightarrow (H_3C)_3C{-}OCH_3 \quad + \quad HCl$$

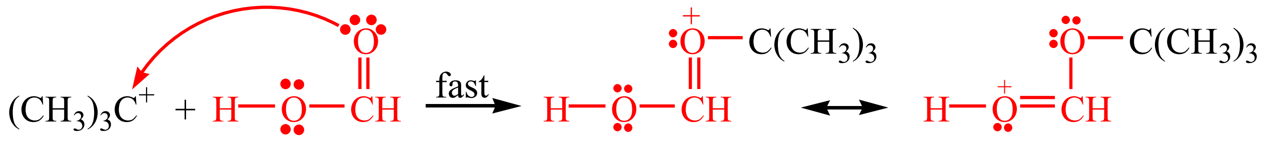
$$(H_3C)_3C{-}Cl \quad + \quad HC(=O)OH \longrightarrow (H_3C)_3C{-}OC(=O)H \quad + \quad HCl$$

2. Solvolysis involves the initial formation of a carbocation and the subsequent reaction of that cation with a molecule of the solvent:

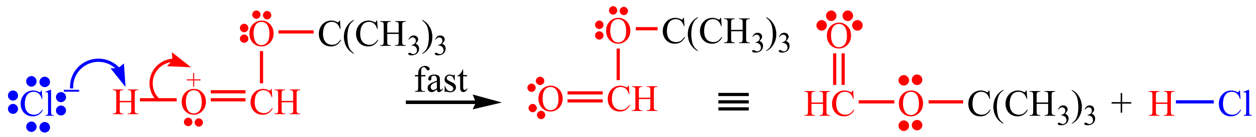
Step 1



Step 2



Step 3



6.14 Factors Affecting the Rates of S_N1 and S_N2 Reactions

1. Factors Influencing the rates of S_N1 and S_N2 reactions:
   1) The **structure** of the **substrate**.
   2) The **concentration** and **reactivity** of the **nucleophile** (for bimolecular reactions).
   3) The **effect** of the **solvent**.
   4) The **nature** of the **leaving group**.

6.14A The Effect of the Structure of the Substrate

1. S_N2 Reactions:

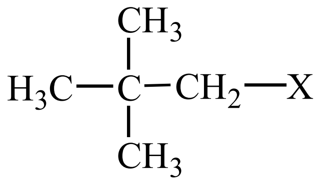
1) Simple alkyl halides show the following general order of reactivity in S_N2 reactions:

methyl > 1° > 2° >> 3° (unreactive)

Table 6.4 **Relative Rates of Reactions of Alkyl Halides in S_N2 Reactions**

Substituent	Compound	Relative Rate
Methyl	CH_3X	30
1°	CH_3CH_2X	1
2°	$(CH_3)_2CHX$	0.02
Neopentyl	$(CH_3)_3CCH_2X$	0.00001
3°	$(CH_3)_3CX$	~0

i) Neopentyl halids are primary halides but are **very unreactive**.



A neopentyl halide

2) **Steric effect:**

i) A **steric effect** is an effect on relative rates caused by the **space-filling properties** of those parts of a molecule **attached at or near** the **reacting site**.

ii) **Steric hindrance:** the spatial arrangement of the atoms or groups at or near the reacting site of a molecule **hinders or retards** a reaction.

iii) Although most molecules are reasonably flexible, very large and bulky groups can often hinder the formation of the required transition state.

3) An S_N2 reaction requires an approach by the nucleophile to a distance within bonding range of the carbon atom bearing the leaving group.

i) Substituents on or near the reacting carbon have a **dramatic inhibiting effect**.

ii) Substituents cause the free energy of the required transition state to be increased and, consequently, they increase the free energy of activation for the reaction.

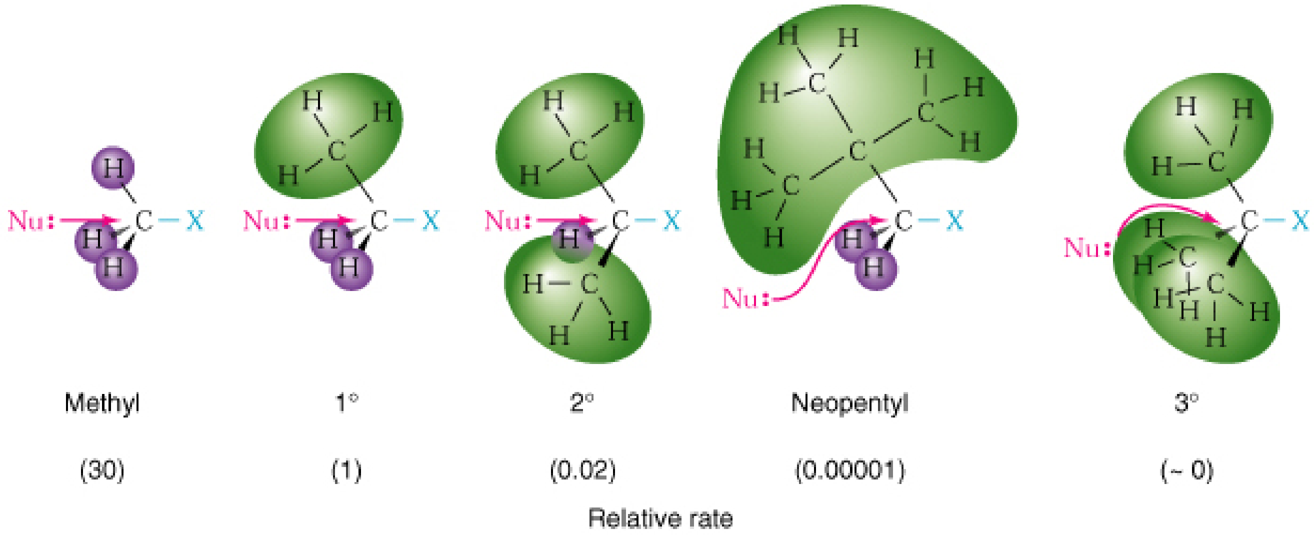
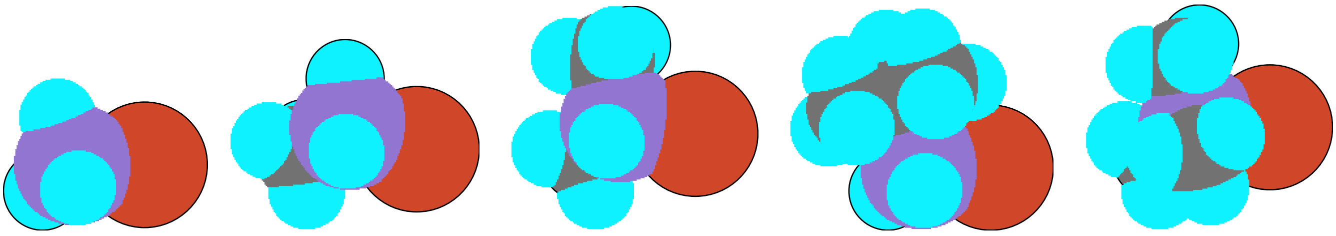


Figure 6.11 **Steric effects in the S_N2 reaction.**



CH_3–Br **CH_3CH_2–Br** **$(CH_3)_2CH$–Br** **$(CH_3)_3CCH_2$–Br** **$(CH_3)_3C$–Br**

2. S_N1 Reactions:

1) **The primary factor that determines the reactivity of organic substrates in an S_N1 reaction is the relative stability of the carbocation that is formed.**

Table 6A **Relative rates of reaction of some alkyl halides with water:**

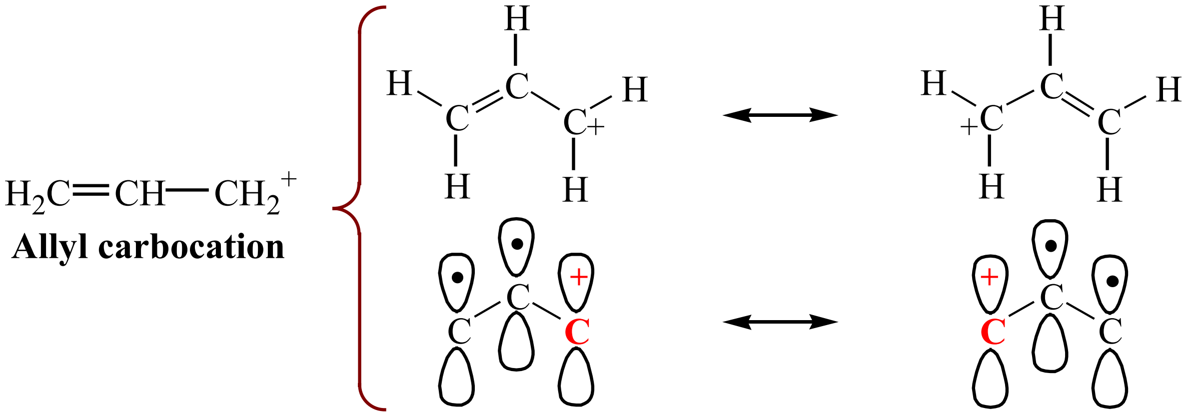
Alkyl halide	Type	Product	Relative rate of reaction
CH_3Br	Methyl	CH_3OH	1.0
CH_3CH_2Br	1°	CH_3CH_2OH	1.0
$(CH_3)_2CHBr$	2°	$(CH_3)_2CHOH$	12
$(CH_3)_3CBr$	3°	$(CH_3)_3COH$	1,200,000

2) Organic compounds that **are capable of forming relatively stable carbocation** can undergo S_N1 reaction at a reasonable rate.

i) Only **tertiary halides** react by an S_N1 mechanism for **simple alkyl halides**.

ii) ***Allylic halides*** and ***benzylic halides***: A ***primary*** allylic or benzylic carbocation is approximately as stable as a ***secondary*** alkyl carbocation (2° allylic or benzylic carbocation is about as stable as a 3° alkyl carbocation).

iii) The stability of allylic and benzylic carbocations: **delocalization**.



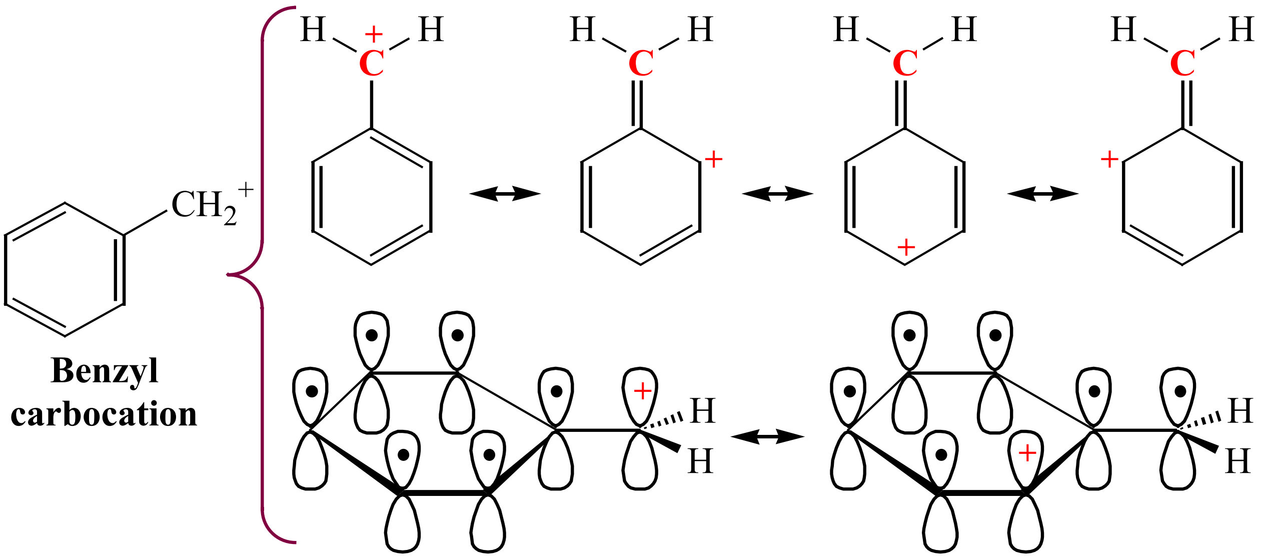


Table 10B **Relative rates of reaction of some alkyl tosylates with ethanol at 25 °C**

Alkyl tosylate	*Product*	*Relative rate*
CH_3CH_2OTos	$CH_3CH_2OCH_2CH_3$	1
$(CH_3)_2CHOTos$	$(CH_3)_2CHOCH_2CH_3$	3
$H_2C{=}CHCH_2OTos$	$H_2C{=}CHCH_2OCH_2CH_3$	35
$C_6H_5CH_2OTos$	$C_6H_5CH_2OCH_2CH_3$	400
$(C_6H_5)_2CHOTos$	$(C_6H_5)_2CHOCH_2CH_3$	10^5
$(C_6H_5)_3COTos$	$(C_6H_5)_3COCH_2CH_3$	10^{10}

4) The stability order of carbocations is exactly the order of S_N1 reactivity for alkyl halides and tosylates.

5) **The order of stability of carbocations:**

3°	>	**2°**	≈	**Allyl**	≈	**Benzyl**	>>	**1°**	>	**Methyl**
R_3C^+	>	R_2CH^+	≈	$H_2C=CH–CH_2^+$	≈	$C_6H_5–CH_2$	>>	RCH_2^+	>	CH_3^+

6) Formation of **a relatively stable carbocation is important in an S_N1 reaction** ⇒ **low free energy of activation** ($\Delta G^‡$) for the slow step of the reaction.

i) The $\Delta G°$ for the first step is positive (***uphill in terms of free energy***) ⇒ the first step is ***endothermic*** ($\Delta H°$ is positive; ***uphill in terms of enthalpy***).

7) The **Hammond-Leffler postulate**:

i) ***The structure of a transition state resembles the stable species that is nearest it in free energy*** ⇒ Any factor that stabilize a high-energy intermediate should also stabilize the transition state leading to that intermediate.

ii) The transition state of a highly **endergonic** step lies close to the products in free energy ⇒ **it resembles the products of that step in structure**.

iii) The transition state of a highly **exergonic** step lies close to the reactants in free energy ⇒ **it resembles the reactants of that step in structure**.

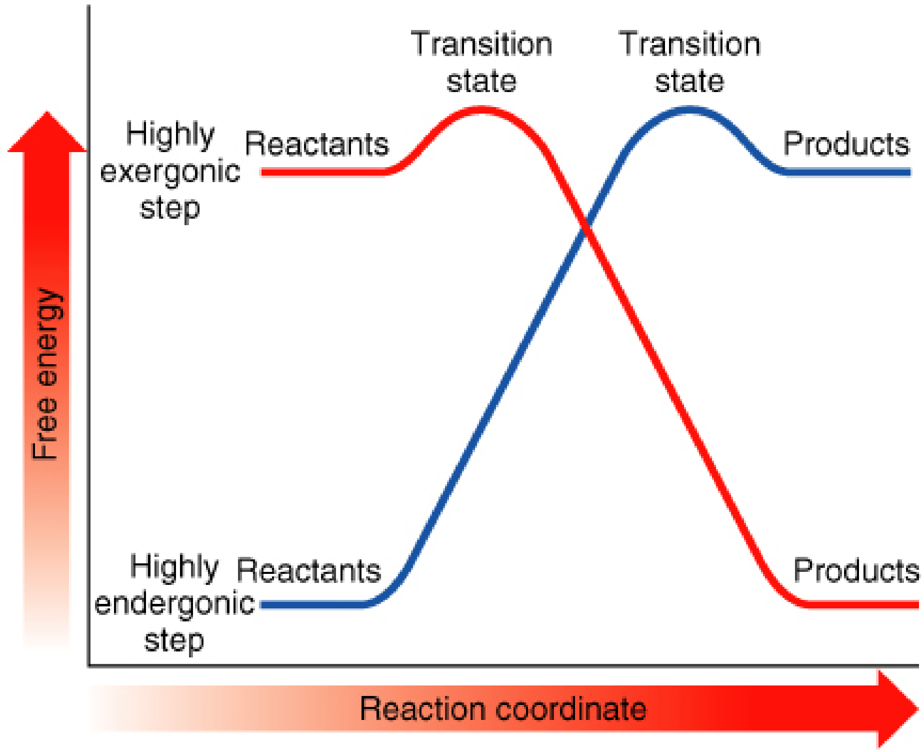
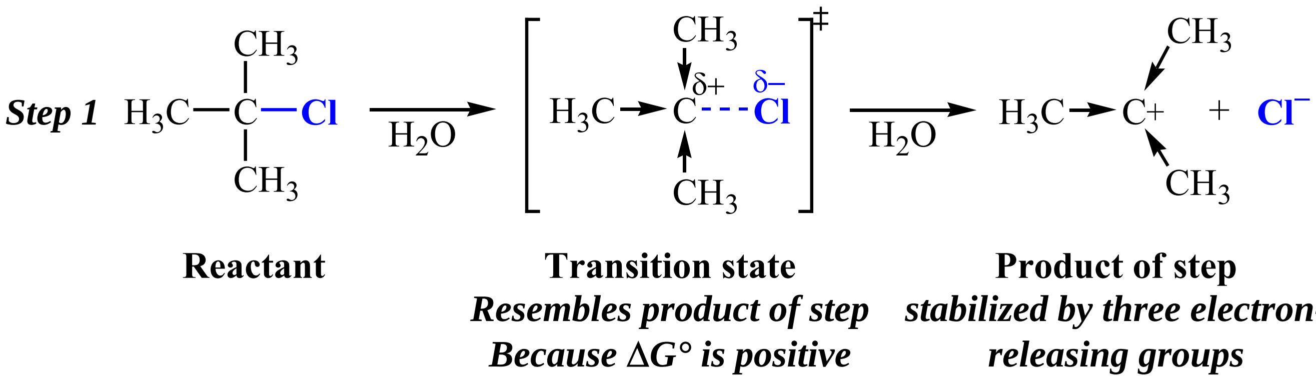


Figure 6.12 Energy diagrams for highly exergonic and highly endergonic steps of reactions.

7) The transition state of the first step in an S_N1 reaction resembles to the product of that step:



i) Any factor that stabilizes the carbocation —— such as delocalization of the positive charge by electron-releasing groups —— should also stabilize the transition state in which the positive charge is developing.

8) The activation energy for an S_N1 reaction of a simple methyl, primary, or secondary halide is so large that, for all practical purposes, an S_N1 reaction does not compete with the corresponding S_N2 reaction.

6.14B The Effect of the Concentration and Strength of the Nucleophile

1. Neither the concentration nor the structure of the nucleophile affects the rates of S_N1 reactions since the nucleophile does not participate in the rate-determining step.

2. The rates of S_N2 reactions depend on both the concentration and the structure of the nucleophile.

3. **Nucleophilicity:** the ability for a species for a **C** atom in the S_N2 reaction.
   1) It depends on **the nature of the substrate** and **the identity of the solvent**.
   2) Relative nucleophilicity (on a ***single*** substrate in a ***single*** solvent system):
   3) Methoxide ion is a good nucleophile (reacts rapidly with a given substrate):

$$CH_3O^- + CH_3I \xrightarrow{\text{rapid}} CH_3OCH_3 + I^-$$

   4) Methanol is a poor nucleophile (reacts slowly with the same substrate under the same reaction conditions):

$$CH_3OH + CH_3I \xrightarrow{\text{very slow}} CH_3\overset{+}{O}(H)CH_3 + I^-$$

   5) The S_N2 reactions of bromomethane with nucleophiles in aqueous ethanol:

$$Nu^- + CH_3Br \longrightarrow NuCH_3 + Br^-$$

Nu =	HS^-	CN^-	I^-	CH_3O^-	HO^-	Cl^-	NH_3	H_2O
Relative reactivity	125,000	125,000	100,000	25,000	16,000	1,000	700	1

4. **Trends in nucleophilicity:**
   1) Nucleophiles that have the **same attacking atom**: **nucleophilicity roughly parallels basicity**.

i) A negatively charged nucleophile is always a more reactive nucleophile than its conjugate acid ⇒ HO^- is a better nucleophile than H_2O; RO^- is a better nucleophile than ROH.

ii) In a group of nucleophiles in which the nucleophilic atom is the same, nucleophilicities parallel basicities:

$$RO^- > HO^- \gg RCO_2^- > ROH > H_2O$$

2) Correlation between electrophilicity-nucleophilicity and Lewis acidity-basicity:

i) "**Nucleophilicity**" measures the affinity (or how rapidly) of a Lewis base for a carbon atom in the S_N2 reaction (relative rates of the reaction).

ii) "**Basicity**", as expressed by pK_a, measures the affinity of a base for a proton (or the position of an acid-base equilibrium).

Correlation between Basicity and Nucleophilicity

Nucleophile	CH_3O^-	HO^-	$CH_3CO_2^-$	H_2O
Rates of S_N2 reaction with CH_3Br	25	16	0.3	0.001
pK_a of conjugate acid	15.5	15.7	4.7	–1.7

iii) A HO^- (pK_a of H_2O is 15.7) is a stronger base than a CN^- (pK_a of HCN is ~10) but CN^- is a stronger nucleophile than HO^-.

3) Nucleophilicity usually increases in going down a column of the periodic table.

i) HS^- is more nucleophilic than HO^-.

ii) The halide reactivity order is: $I^- > Br^- > Cl^-$

iii) Larger atoms are more **polarizable** (their electrons are more easily distorted) ⇒ a larger nucleophilic atom can donate a greater degree of electron density to the substrate than a smaller nucleophile whose electrons are more tightly held.

6.14C Solvent Effects on S_N2 Reactions: Protic and Aprotic Solvents

1. **Protic Solvents:** ***hydroxylic solvents*** such as **alcohols** and **water**

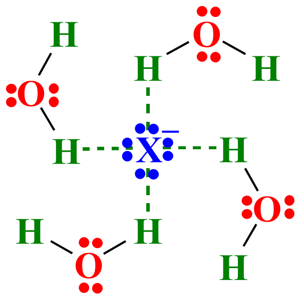
1) The solvent molecule has **a hydrogen atom attached to an atom of a strongly electronegative element**.

2) In protic solvents, the nucleophile with **larger nucleophilic atom** is **better**.

i) Thiols (**R–SH**) are stronger nucleophiles than alcohols (**R–OH**); **RS⁻** ions are more nucleophilic than **RO⁻** ions.

ii) The order of reactivity of halide ions: **$I^- > Br^- > Cl^- > F^-$**

3) Molecules of protic solvents form **hydrogen bonds nucleophiles**:



Molecules of the protic solvent, water, solvate a halide ion by forming hydrogen bonds to it.

i) A small nucleophile, such fluoride ion, because its charge is more concentrated, is strongly solvated than a larger one.

4) ***Relative Nucleophilicity in Protic Solvents:***

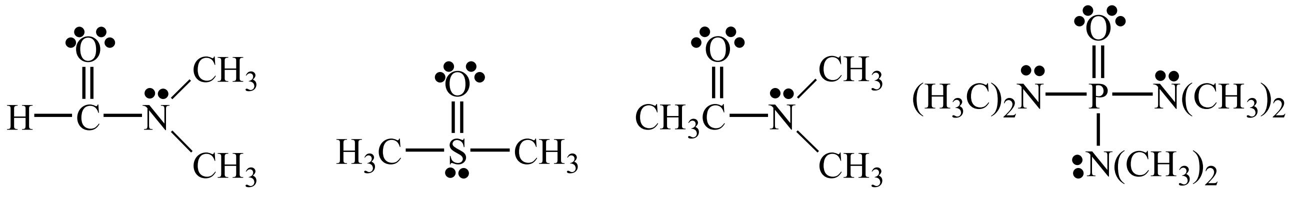
$$SH^- > CN^- > I^- > HO^- > N_3^- > Br^-\ CH_3CO_2^- > Cl^- > F^- > H_2O$$

2. Polar Aprotic Solvent:

1) **Aprotic solvents** are those solvents whose molecules do not have **a hydrogen atom attached to an atom of a strongly electronegative element**.

i) Most aprotic solvents (benzene, the alkanes, *etc.*) are relatively nonpolar, and they do not dissolve most ionic compounds.

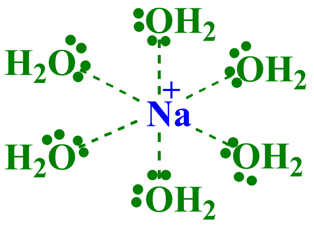
ii) Polar aprotic solvents are ***especially useful*** in S_N2 reactions:



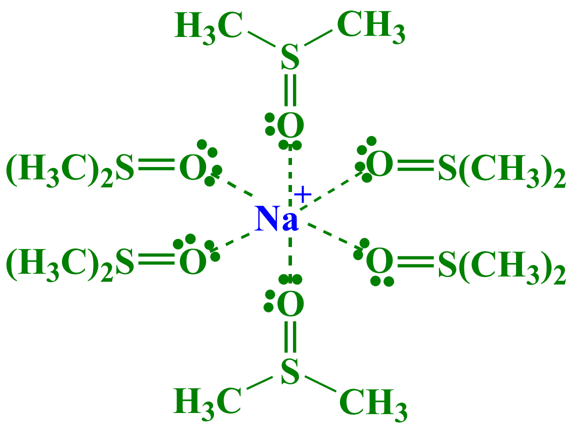
***N,N*-Dimethylformamide** **Dimethyl sulfoxide** **Dimethylacetamide** **Hexamethylphosphoramide**

(DMF) (DMSO) (DMA) (HMPA)

1) **Polar aprotic solvents** dissolve ionic compounds, and they **solvate cations** very well.



A sodium ion solvated by molecules of the protic solvent water



A sodium ion solvated by molecules of the aprotic solvent dimethyl sulfoxide

2) **Polar aprotic solvents do not solvate anions to any appreciable extent** because they **cannot form hydrogen bonds** and because **their positive centers are well shielded from any interaction with anions**.

i) **"Naked" anions are highly reactive both as bases and nucleophiles.**

ii) The relative order of reactivity of halide ions is the same as their relative basicity in DMSO:

$$F^- > Cl^- > Br^- > I^-$$

iii) The relative order of reactivity of halide ions in alcohols or water:

$$I^- > Br^- > Cl^- > F^-$$

3) **The rates of S_N2 reactions generally are vastly increased when they are carried out in polar aprotic solvents.**

4) **Solvent effects on the S_N2 reaction of azide ion with 1-bromobutane:**

$$N_3^- + CH_3CH_2CH_2CH_2Br \xrightarrow{\text{Solvent}} CH_3CH_2CH_2CH_2N_3 + Br^-$$

Solvent	HMPA	CH_3CN	DMF	DMSO	H_2O	CH_3OH

Relative reactivity	**200,000**	**5,000**	**2,800**	**1,300**	**6.6**	**1**

6.14D SOLVENT EFFECTS ON S_N1 REACTIONS: THE IONIZING ABILITY OF THE SOLVENTS

1. **Polar protic solvent** will greatly increase the rate of ionization of an alkyl halide ***in any S_N1 reaction***.
   1) Polar protic solvents **solvate cations** and **anions effecttively**.
   2) Solvation **stabilizes the transition state** leading to the intermediate carbocation and **halide ion** more it does the **reactants** ⇒ the **free energy of activation** is **lower**.
   3) The transition state for the ionization of organohalide resembles the product carbocation.

$$(H_3C)_3C{-}Cl \longrightarrow \left[(H_3C)_3\overset{\delta+}{C}\text{- -}\overset{\delta-}{Cl} \right]^{\ddagger} \longrightarrow (CH_3)_3C^{+} + Cl^{-}$$

Reactant | **Transition state** | **Products**

Separated charges are developing

2. **Dielectric constant:** a measure of a solvent's ability to insulate opposite charges from each other.

Table 6.5 Dielectric Constants of Some Common Solvents

Name	Structure	Dielectric constant, ε
APROTIC (NONHYDROXYLIC) SOLVENTS		
Hexane	$CH_3CH_2CH_2CH_2CH_2CH_3$	1.9
Benzene	C_6H_6	2.3
Diethyl ether	$CH_3CH_2–O–CH_2CH_3$	4.3
Chloroform	$CHCl_3$	4.8
Ethyl acetate	$CH_3C(O)OC_2H_5$	6.0
Acetone	$(CH_3)_2CO$	20.7
Hexamethylphosphoramide (HMPA)	$[(CH_3)_2N]_3PO$	30
Acetonitrile	CH_3CN	36
Dimethylformamide (DMF)	$(CH_3)_2NCHO$	38
Dimethyl sulfoxide (DMSO)	$(CH_3)_2SO$	48
PROTIC (HYDROXYLIC) SOLVENTS		
Acetic acid	$CH_3C(O)OH$	6.2
tert-Butyl alcohol	$(CH_3)_3COH$	10.9
Ethanol	CH_3CH_2OH	24.3
Methanol	CH_3OH	33.6
Formic acid	$HC(O)OH$	58.0
Water	H_2O	80.4

1) Water is the most effective solvent for promoting ionization, but most organic compounds do not dissolve appreciably in water.
2) Methanol-water and ethanol-water are commonmixed solvents for nucleophilic substitution reactions.

Table 6C **Relative rates for the reaction of 2-chloro-2-methylpropane with different solvents**

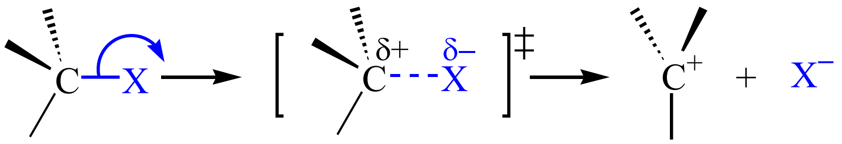
Solvent	Relative rate
Ethanol	1
Acetic acid	2
Aqueous ethanol (40%)	100
Aqueous ethanol (80%)	14,000
Water	105

6.14E THE NATURE OF THE LEAVING GROUP

1. **Good Leaving Group:**
   1) The **best leaving groups** are those that become the **most stable ions** after they depart.
   2) Most leaving groups leave as a negative ion ⇒ the best leaving groups are those ions that stabilize a negative charge most effectively ⇒ the best leaving groups are weak bases.

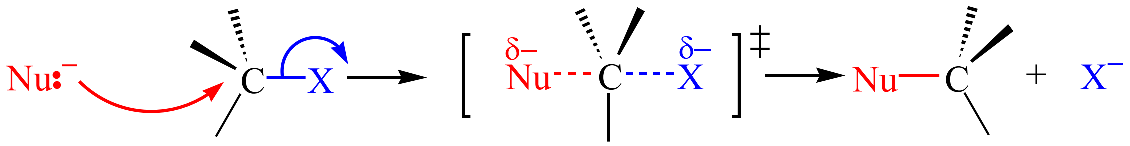
2. **The leaving group** begins to acquire a negative charge as the transition state is reached in either an S_N1 or S_N2 reaction.

S_N1 Reaction (rate-limiting step)



Transition state

S_N2 Reaction



Transition state

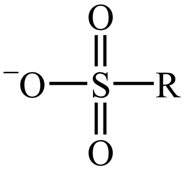
1) Stabilization of the developing negative charge at the leaving group stabilizes

the transition state (lowers its free energy) ⇒ lowers the free energy of activation ⇒ increases the rate of the reaction.

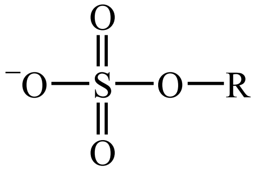
3. **Relative reactivity of some leaving groups:**

Leaving group	TosO⁻	I⁻	Br⁻	Cl⁻	F⁻	HO⁻, H_2N^-, RO⁻
Relative reactivity	60,000	30,000	10,000	200	1	~0

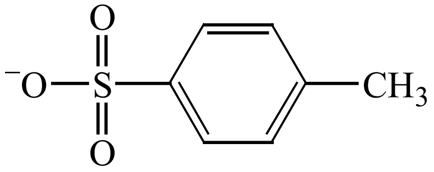
4. **Other good leaving groups:**



An alkanesulfonate ion



An alkyl sulfate ion

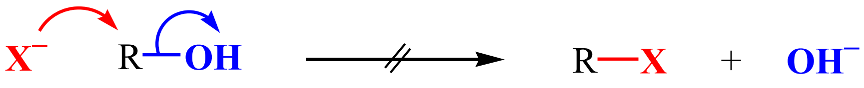


***p*-Toluenesulfonate ion**

1) These anions are all the conjugate bases of very strong acids.
2) The trifluoromethanesulfonate ion ($CF_3SO_3^-$, **triflate ion**) is one of the best leaving group known to chemists.
   i) It is the anion of CF_3SO_3H, an exceedingly strong acid — one that is much stronger than sulfuric acid.

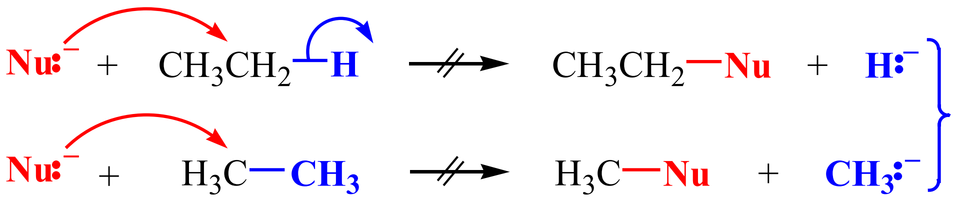
$CF_3SO_3^-$, **triflate ion**
(**a "super" leaving group**)

5. **Strongly basic ions rarely act as leaving groups**.



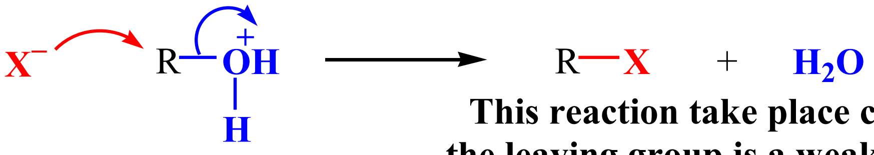
This reaction doesn't take place because the leaving group is a strongly basic hydroxide ion.

1) Very powerful bases such as hydride ions (**H:**⁻) and alkanide ions (**R:**⁻) virtually never act as leaving groups.



These are not leaving groups

6. **Protonation** of an alcohol with a strong acid turns its poor OH^- leaving group (strongly basic) into a **good leaving group** (**neutral water molecule**).



This reaction take place cause the leaving group is a weak base.

6.14F SUMMARY: S_N1 VERSUS S_N2

1. Reactions of alkyl halides by an S_N1 mechanism are favored by the use of:
   1) substrates that can form relatively stable carbocations.
   2) weak nucleophiles.
   3) highly ionizing solvent.

2. Reactions of alkyl halides by an S_N2 mechanism are favored by the use of:
   1) relatively unhindered alkyl halides.
   2) strong nucleophiles.
   3) polar aprotic solvents.
   4) high concentration of nucleophiles.

3. The effect of the leaving group is the same in both S_N1 and S_N2:

R–I > R–Br > R–Cl **S_N1** or **S_N2**

Table 6.6 Factors Favoring S_N1 versus S_N2 Reactions

Factor	**S_N1**	**S_N2**
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile
Solvent	Polar protic (e.g. alcohols, water)	Polar aprotic (e.g. DMF, DMSO)
Leaving group	I > Br > Cl > F for both S_N1 and S_N2 (the weaker the base after departs, the better the leaving group)	

6.15 Organic Synthesis: Functional Group Transformations Using S_N2 Reactions

1. **Functional group transformation (interconversion): (Figure 6.13)**

2. Alkyl chlorides and bromides are easily converted to alkyl iodide by S_N2 reaction

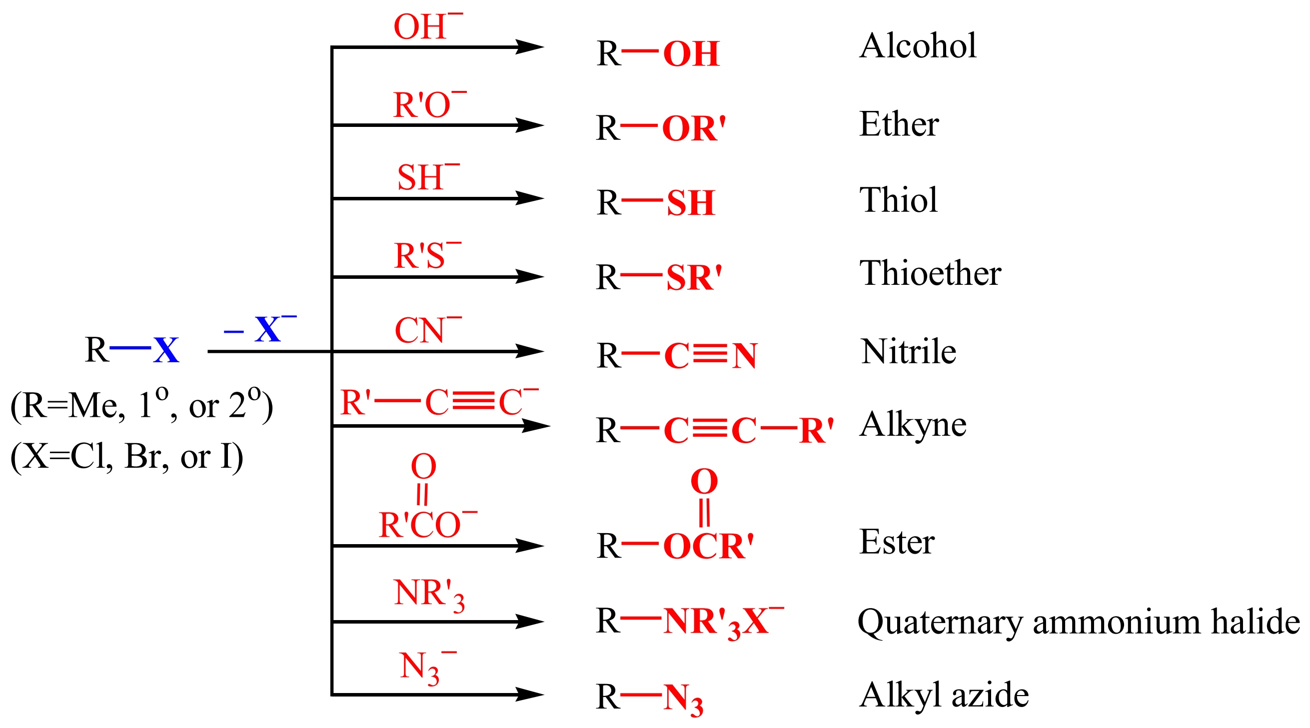
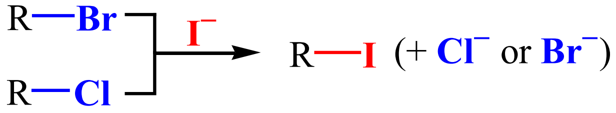
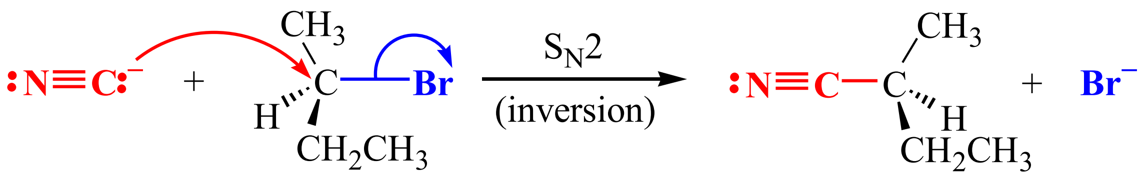


Figure 6.13 Functional group interconversions of methyl, primary, and secondary alkyl halides using S_N2 reactions.



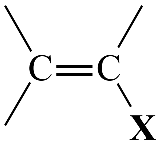
3. **Inversion of configuration** in **S_N2 reactions**:



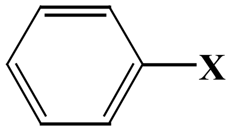
(*R*)-2-Bromobutane **(*S*)-2-Methylbutanenitrile**

6.15A The Unreactivity of Vinylic and Phenyl Halides

1. Vinylic halides and phenyl halides are generally unreactive in S_N1 or S_N1 reactions.
   1) Vinylic and phenyl cations are highly unstable and do not form readily.
   2) The C–X bond of a vinylic or phenyl halide is stronger than that of an alkyl halide and the electrons of the double bond or benzene ring repel the approach of a nucleophile from the back side.



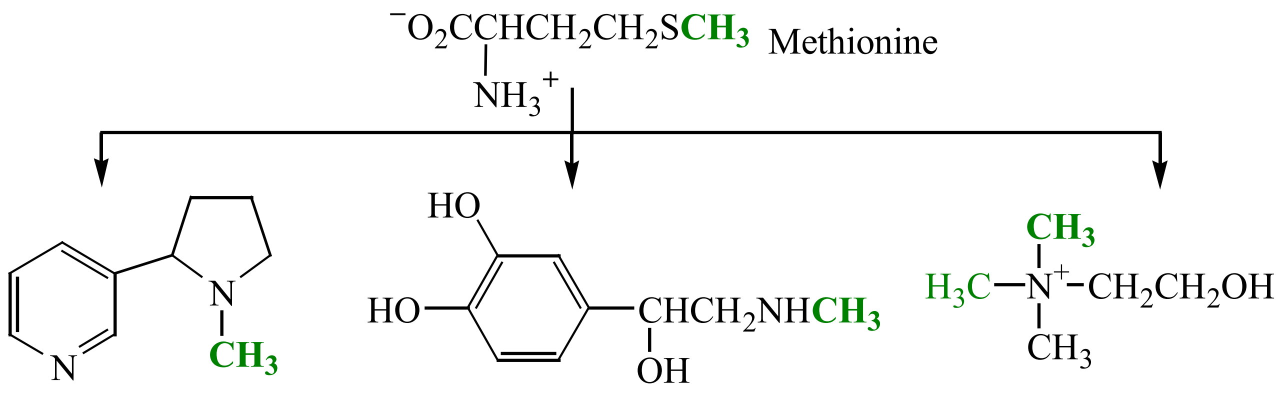
A vinylic halide



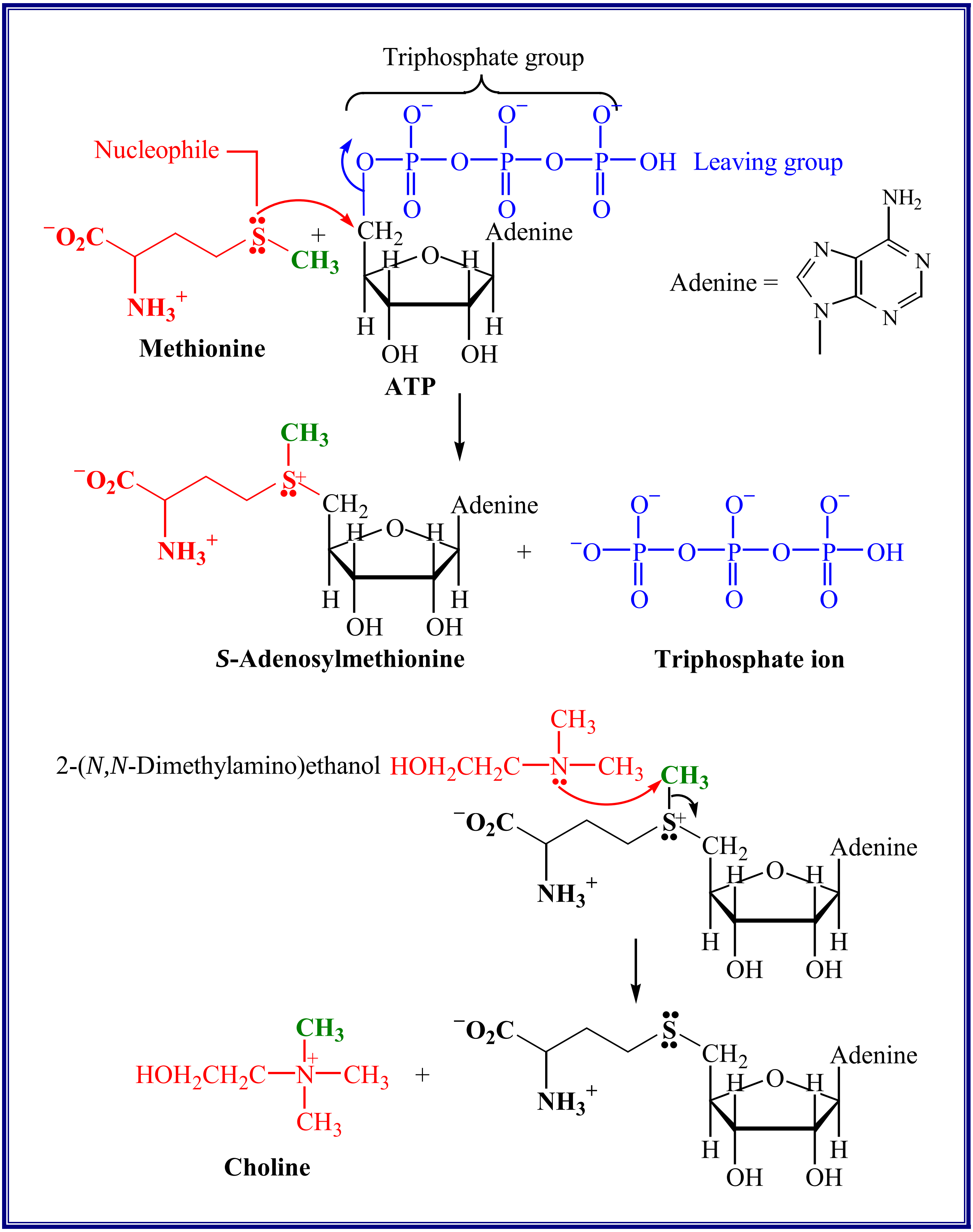
Phenyl halide

The Chemistry of….

Biological Methylation: A Biological Nucleophilic Substitution Reaction

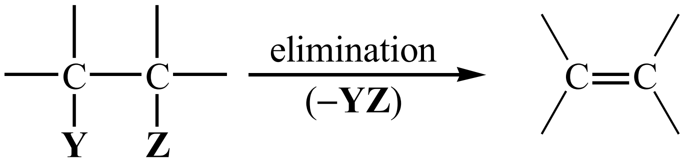


Nicotine **Adrenaline** **Choline**



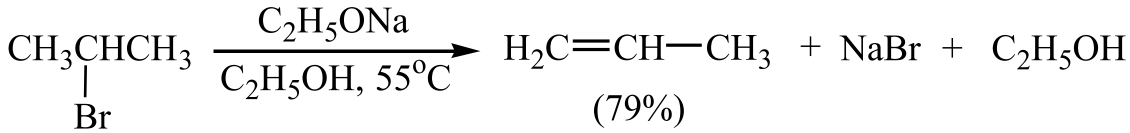
Triphosphate group
Nucleophile
Leaving group
Methionine
ATP
Adenine =
S-Adenosylmethionine
Triphosphate ion
2-(N,N-Dimethylamino)ethanol
Choline

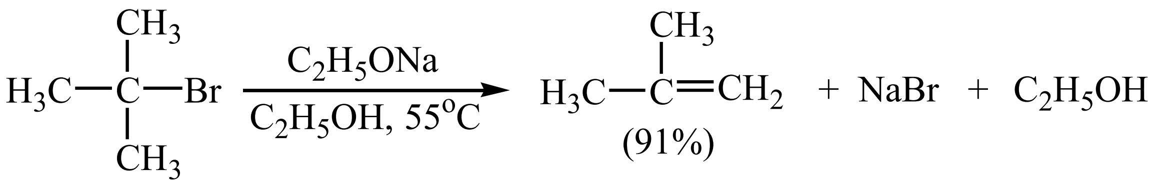
6.16 ELIMINATION REACTIONS OF ALKYL HALIDES



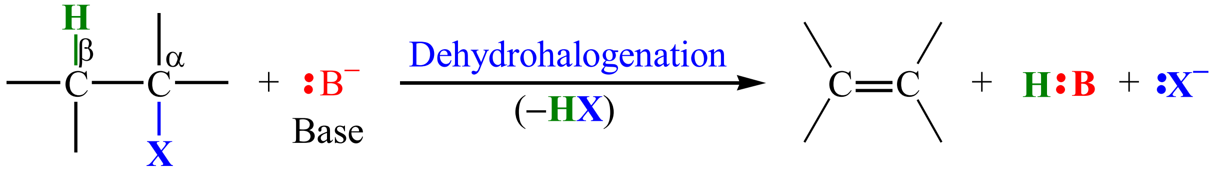
6.16A DEHYDROHALOGENATION

1. Heating an alkyl halide with a strong base causes elimination to happen:





2. **Dehydrohalogenation:**

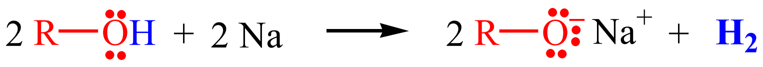


X = Cl, Br, I

1) alpha (α) carbon atom:
2) beta (β) hydrogen atom:
3) β-elimination (1,2-elimination):

6.16B BASES USED IN DEHYDROHALOGENATION

1. Potassium hydroxide dissolved in ethanol and the sodium salts of alcohols (such as sodium ethoxide) are often used as the base for dehydrohalogenation.
   1) The sodium salt of an alcohol (a sodium alkoxide) can be prepared by treating an alcohol with sodium metal:

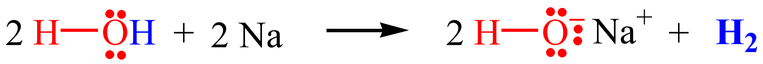


Alcohol **sodium alkoxide**

i) This is an **oxidation-reduction reaction**.

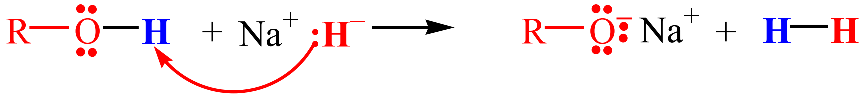
ii) Na is a very powerful reducing agent.

iii) Na reacts vigorously (at times explosively) with water:



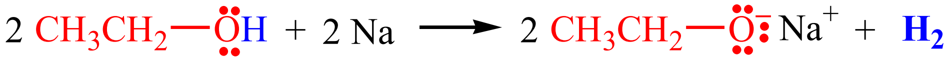
sodium hydroxide

2) Sodium alkoxides can also be prepared by reacting an alcohol with sodium hydride ($H:^-$):



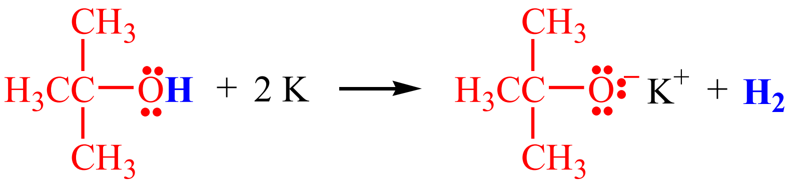
2. Sodium (and potassium) alkoxides are usually prepared by using excess of alcohol, and the excess alcohol becomes the solvent for the reaction.

1) Sodium ethoxide:



Ethanol (excess) **sodium ethoxide**

2) Potassium *tert*-butoxide:



***tert*-Butyl alcohol (excess)** **Potassium *tert*-butoxide**

6.16C MECHANISMS OF DEHYDROHALOGENATIONS

1. **E2 reaction**
2. **E1 reaction**

6.17 THE E2 REACTION

1. Rate equation

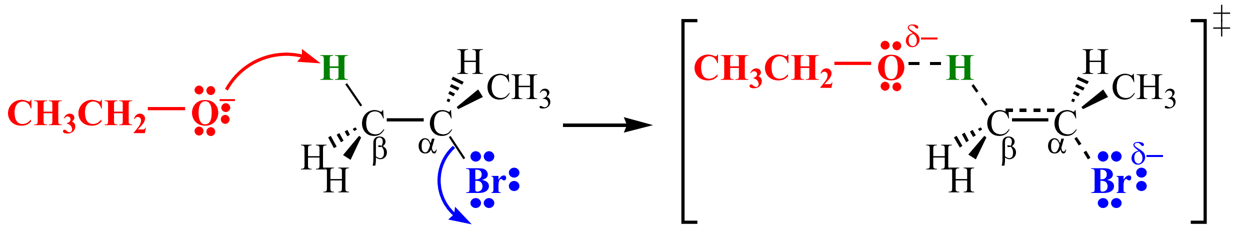
$$\text{Rate} = k\,[CH_3CHBrCH_3]\,[C_2H_5O^-]$$

A Mechanism for the E2 Reaction

Reaction:

$$C_2H_5O^- + CH_3CHBrCH_3 \longrightarrow CH_2{=}CHCH_3 + C_2H_5OH + Br^-$$

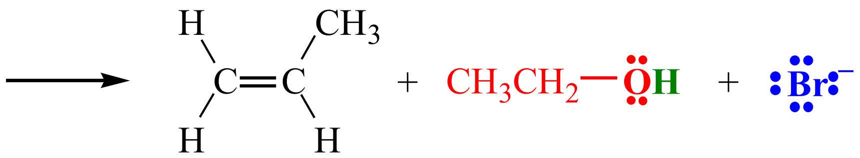
Mechanism:



Transition state

The basic ethoxide ion begins to remove a proton from the β-carbon using its electron pair to form a bond to it. At the same tim, the electron pair of the β C–H bond begins to move in to become the π bond of a double bond, and the bromide begins to depart with the electrons that bonded it to the α carbon.

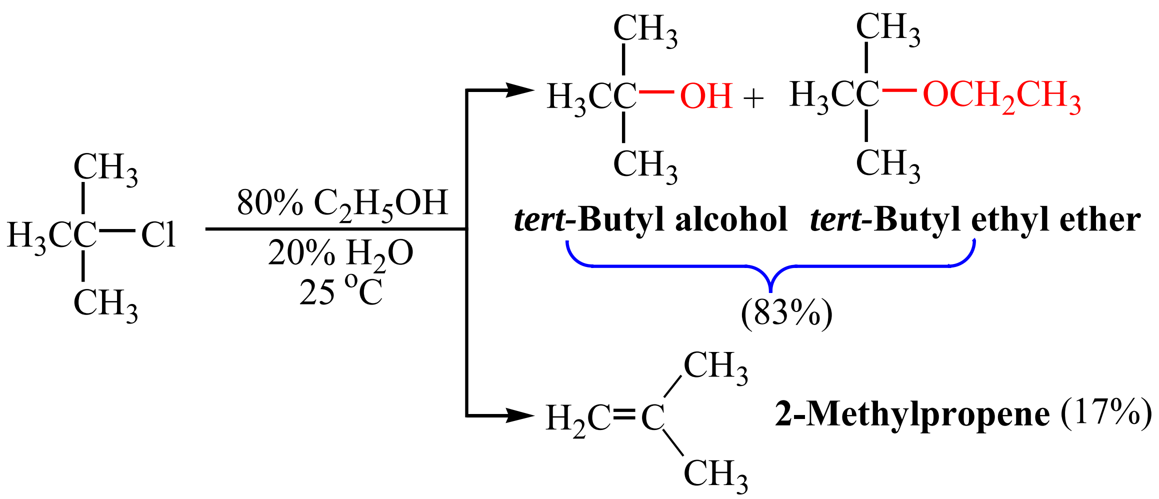
Partial bonds now exist between the oxygen and the β hydrogen and between the α carbonand the bromine. The carbon-carbon bond is developing double bond character.



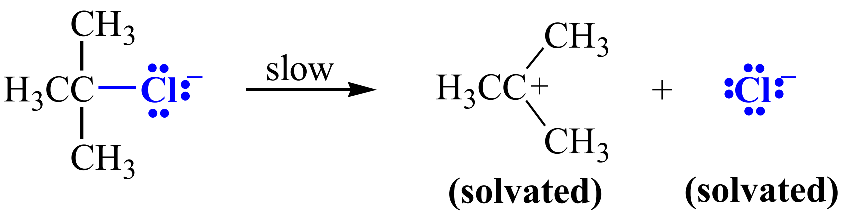
Now the double bond of the alkene is fully formed and the alkene has a trigonal plannar geometry at each carbon atom. The other products are a molecule of ethanol and a bromide ion.

6.18 THE E1 REACTION

1. Treating *tert*-butyl chloride with 80% aqueous ethanol at 25°C gives ***substitution products*** in 83% yield and an ***elimination product*** in 17% yield.

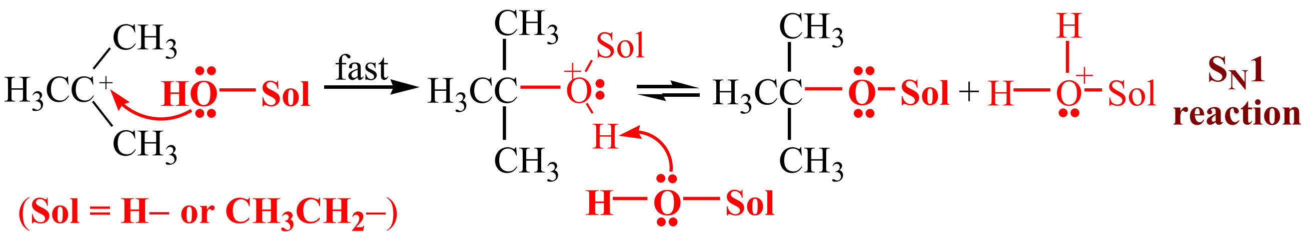


1) The initial step for reactions is the formation of a *tert*-butyl cation.

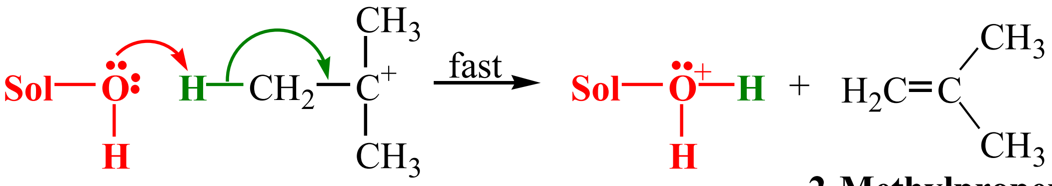


2) Whether substitution or elimination takes place depends on the next step (the fast step).

i) The S_N1 reaction:



ii) The E1 reaction:



E1 reaction

2-Methylpropene

iii) The E1 reaction almost always accompany S_N1 reactions.

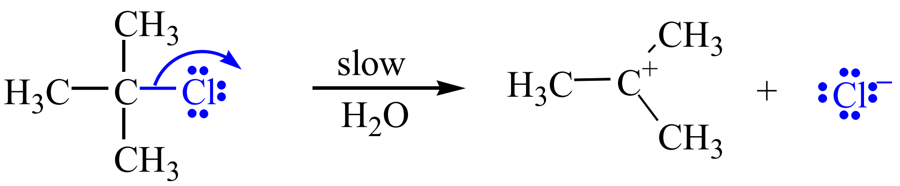
A Mechanism for the E1 Reaction

Reaction:

$$(CH_3)_3CBr \quad + \quad H_2O \quad \longrightarrow \quad CH_2{=}C(CH_3)_3 \quad + \quad H_2O^+ \quad + \quad Cl^-$$

Mechanism:

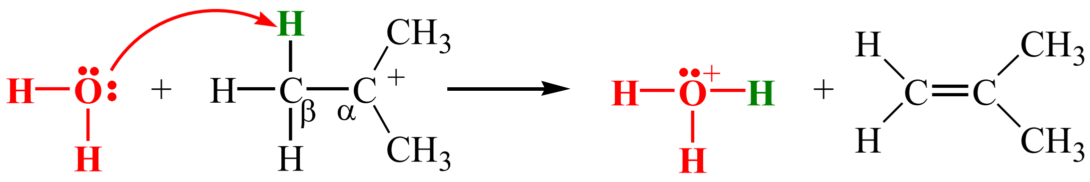
Step 1



Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3^0 carbocatoin and a chloride ion. The ions are solvated(and stabilized) by surrounding water molecules.

Step 2



A molecule of water removes one of the hydrogens from the β carbon of the carbocation. An electron pair moves in to form a double bond between the α and β carbon atoms.

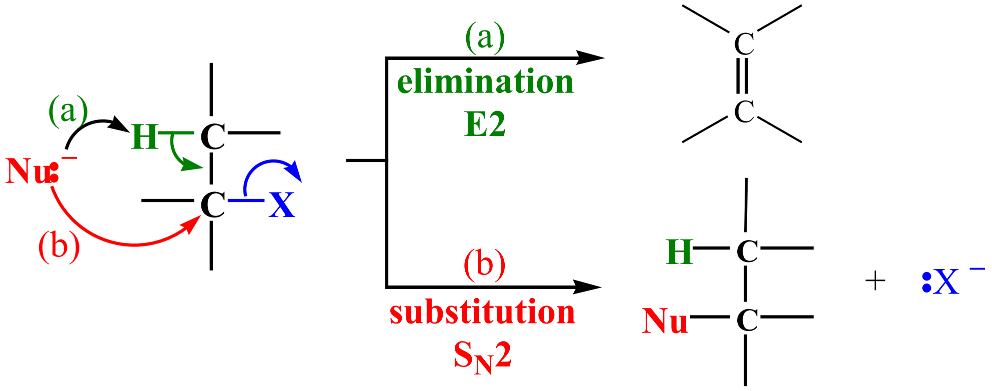
This step produces the alkene and a hydronium ion

6.19 SUBSTITUTION VERSUS ELIMINATION

1. Because the reactive part of a nucleophile or a base is an unshared electron pair, all nucleophiles are potential bases and all bases are potential nucleophiles.
2. Nucleophileic substitution reactions and elimination reactions often compete with each other.

6.19A S_N2 VERSUS E2

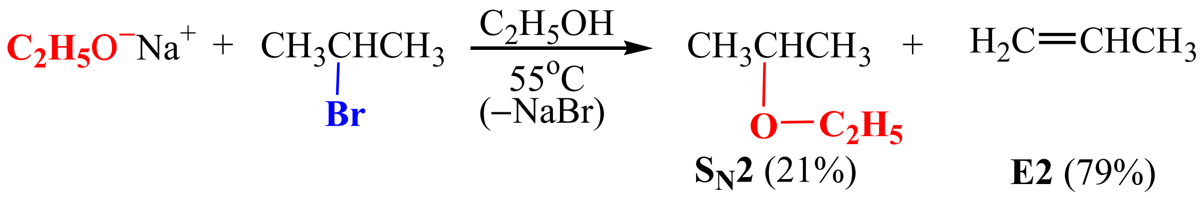
1. Since eliminations occur best by an E2 path when carried out with a high concentration of a strong base (and thus a high concentration of a strong nucleophile), substitution reactions by an S_N2 path often compete with the elimination reaction.
   1) When the nucleophile (base) attacks a β carbon atom, elimination occurs.
   2) When the nucleophile (base) attacks the carbon atom bearing the leaving group, substitution results.



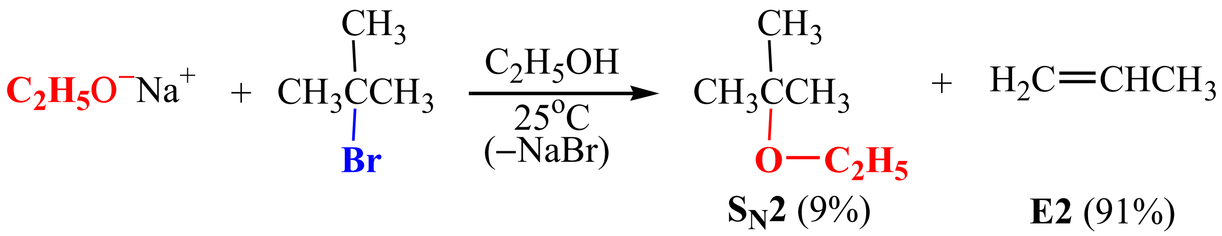
2. ***Primary*** halides and ethoxide: **substitution is favored**

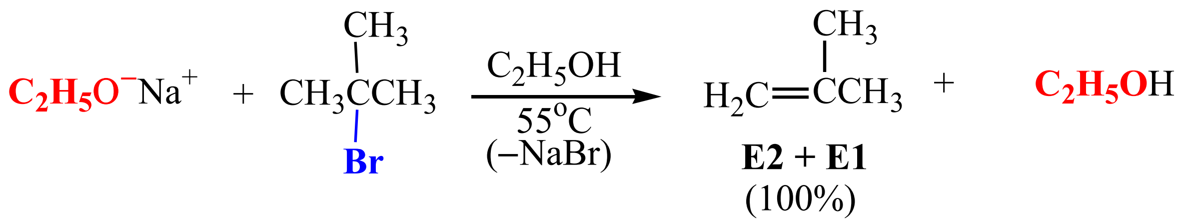
$$CH_3CH_2O^-Na^+ + CH_3CH_2Br \xrightarrow[\substack{55^oC \\ (-NaBr)}]{C_2H_5OH} CH_3CH_2OCH_2CH_3 + H_2C{=}CH_2$$

3. ***Secondary*** halides: **elimination is favored**



4. ***Tertiary*** halides: **no S_N2 reaction, elimination reaction is highly favored**





1) Elimination is favored when the reaction is carried out at higher temperature.
   i) Eliminations have higher free energies of activation than substitutions because eliminations have a greater change in bonding (more bonds are broken and formed).
   ii) Eliminations have higher entropies than substitutions because eliminations have a greater number of products formed than that of starting compounds).
2) Any substitution that occurs must take place through an S_N1 mechanism.

6.19B TERTIARY HALIDES: S_N1 VERSUS E1

1. E1 reactions are favored:
   1) with substrates that can form stable carbocations.
   2) by the use of poor nucleophiles (weak bases).
   3) by the use of polar solvents (high dielectric constant).
2. It is usually difficult to influence the relative position between S_N1 and E1 products.

3. S_N1 reaction is favored over E1 reaction in most unimolecular reactions.

1) In general, substitution reactions of tertiary halides do not find wide use as synthetic methods.

2) Increasing the temperature of the reaction favors reaction by the E1 mechanism at the expense of the S_N1 mechanism.

3) **If elimination product is desired, it is more convenient to add a strong base and force an E2 reaction to take place**.

6.20 OVERALL SUMMARY

Table 6.7 Overall Summary of S_N1, S_N2, E1 and E2 Reactions

CH_3X **Methyl**	**RCH_2X** **1°**	**RR'CHX** **2°**	**RR'R"CX** **3°**
	Bimolecular reactions	**only**	**S_N1/E1 or E2**
Gives S_N2 reactions	Gives mainly S_N2 except with a hindered strong base [e.g., $(CH_3)_3CO^-$] and then gives mainly E2	Gives mainly S_N2 with weak bases (e.g., I^-, CN^-, RCO_2^-) and mainly E2 with strong bases (e.g., RO^-)	No S_N2 reaction. In solvolysis gives S_N1/E1, and at lower temperatures S_N1 is favored. When a strong base (e.g., RO^-) is used E2 predominates

Table 6D Reactivity of alkyl halides toward substitution and elimination

Halide type	*S_N1*	*S_N2*	*E1*	*E2*
Primary halide	Does not occur	**Highly favored**	Does not occur	Occurs when strong, hindered bases are used
Secondary halide	Can occur under solvolysis conditions in polar solvents	**Favored by good nucleophiles in polar aprotic solvents**	Can occur under solvolysis conditions in polar solvents	**Favored when strong bases are used**
Tertiary halide	**Favored by nonbasic nucleophiles in polar solvents**	Does not occur	Occurs under solvolysis conditions	**Highly favored when bases are used**

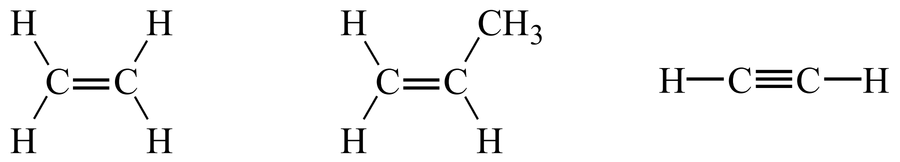
Table 6E Effects of reaction variables on substitution and elimination reactions

Reaction	*Solvent*	*Nucleophile/base*	**Leaving group**	**Substrate structure**
S_N1	**Very strong effect**; reaction favored by polar solvents	**Weak effect**; reaction favored by good nucleophile/weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3°, allylic, and benzylic substrates
S_N2	**Strong effect**; reaction favored by polar aprotic solvents	**Strong effect**; reaction favored by good nucleophile/ weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 1°, allylic, and benzylic substrates
E1	**Very strong effect**; reaction favored by polar solvents	**Weak effect**; reaction favored by weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3°, allylic, and benzylic substrates
E2	**Strong effect**; reaction favored by polar aprotic solvents	**Strong effect**; reaction favored by poor nucleophile/ strong base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3° substrates

ALKENES AND ALKYNES I. PROPERTIES AND SYNTHESIS

7.1 INTRODUCTION

1. Alkenes are hydrocarbons whose molecules contain the C–C double bond.
   1) ***olefin*:**
      i) Ethylene was called olefiant gas (Latin: *oleum*, oil + *facere*, to make) because gaseous ethane (C_2H_4) reacts with chlorine to form $C_2H_4Cl_2$, a liquid (oil).



Ethene **Propene** **Ethyne**

2. Alkynes are hydrocarbons whose molecules contain the C–C triple bond.
   1) ***acetylenes*:**

7.1A PHYSICAL PROPERTIES OF ALKENES AND ALKYNES

1. Alkenes and alkynes have physical properties similar to those of corresponding alkanes.
   1) Alkenes and alkynes up to four carbons (except 2-butyne) are gases at room temperature.
   2) Alkenes and alkynes dissolve in nonpolar solvents or in solvents of low polarity.
      i) Alkenes and alkynes are only ***very slightly soluble*** in water (with alkynes being slightly more soluble than alkenes).
      ii) Alkenes and alkynes have densities lower than that of water.

7.2 NOMENCLATURE OF ALKENES AND CYCLOALKENES

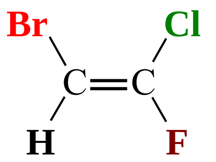
1. Determine the base name by selecting the longest chain that contains the double

bond and change the ending of the name of the alkane of identical length from **-ane** to **-ene**.

2. Number the chain so as to include both carbon atoms of the double bond, and begin numbering at the end of the chain nearer the double bond. Designate the location of the double bond by using the number of the first atom of the double bond as a prefix:
3. Indicate the location of the substituent groups by numbering of the carbon atoms to which they are attached.
4. Number substituted cycloalkenes in the same way that gives the carbon atoms of the double bond the 1 and 2 positions and that also gives the substituent groups the lower numbers at the first point of difference.
5. Name compounds containing a double bond and an alcohol group as alkenols (or cycloalkenols) and give the alcohol carbon the lower number.
6. Two frequently encountered alkenyl groups are the ***vinyl*** group and ***allyl*** group.
7. If two identical groups are on the same side of the double bond, the compound can be designated ***cis***; if they are on the opposite sides it can be designated ***trans***.

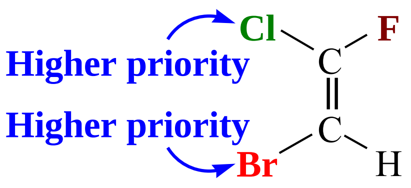
7.2A THE (*E*)-(*Z*) SYSTEM FOR DESIGNATING ALKENE DIASTEREOMERS

1. *Cis*- and *trans*- designations the stereochemistry of alkene diastereomers are unambiguous only when applied to disubstituted alkenes.



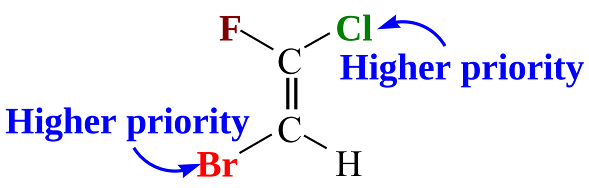
A

2. **The (*E*)-(*Z*) system:**



Cl > F

Br > H

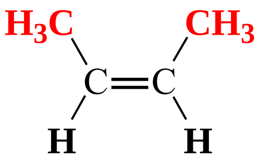


(*Z*)-2-Bromo-1-chloro-1-fluroethene **(*E*)-2-Bromo-1-chloro-1-fluroethene**

1) The group of higher priority on one carbon atom is compared with the group of higher priority on the other carbon atom:

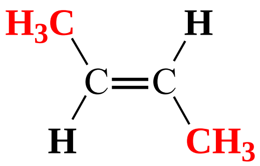
i) (*Z*)-alkene: If the two groups of higher priority are on the same side of the double bond (German: *zusammen*, meaning together).

ii) (*E*)-alkene: If the two groups of higher priority are on opposite side of the double bond (German: *entgegen*, meaning opposite).

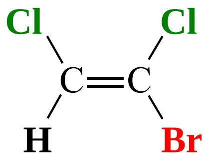


(*Z*)-2-Butene
(*cis*-2-butene)

CH_3 > H

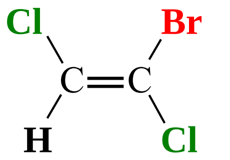


(*E*)-2-Butene
(*trans*-2-butene)



(*E*)-1-Bromo-1,2-dichloroethene

Cl > H
Br > Cl



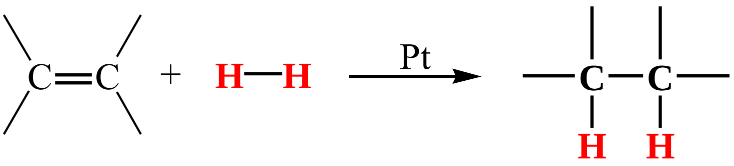
(*Z*)-1-Bromo-1,2-dichloroethene

7.3 RELATIVE STABILITIES OF ALKENES

7.3A HEATS OF HYDROGENATION

1. The reaction of an alkene with hydrogen is an exothermic reaction; the enthalpy change involved is called **the heat of hydrogenation**.

1) Most alkenes have heat of hydrogenation near –120 kJ mol^{-1}.



$\Delta H° \approx -120$ kJ mol^{-1}

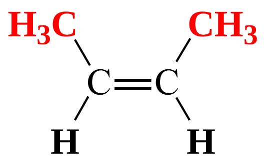
2) Individual alkenes have heats of hydrogenation may differ from this value by more than 8 kJ mol^{-1}.

3) The differences permit the measurement of the relative stabilities of alkene

isomers ***when hydrogenation converts them to the same product***.

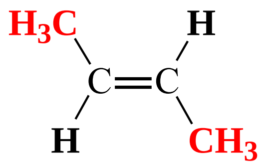
$$CH_3CH_2CH{=}CH_2 + H_2 \xrightarrow{Pt} CH_3CH_2CH_2CH_3 \qquad \Delta H^o = -127\ \text{kJ mol}^{-1}$$

1-Butene (C_4H_8) **Butane**



$$+ H_2 \xrightarrow{Pt} CH_3CH_2CH_2CH_3 \qquad \Delta H^o = -120\ \text{kJ mol}^{-1}$$

***cis*-2-Butene (C_4H_8)** **Butane**



$$+ H_2 \xrightarrow{Pt} CH_3CH_2CH_2CH_3 \qquad \Delta H^o = -115\ \text{kJ mol}^{-1}$$

***trans*-2-Butene (C_4H_8)** **Butane**

2. In each reaction:
   1) The product (butane) is the same.
   2) One of the reactants (hydrogen) is the same.
   3) The different amount of ***heat*** evolved is related to different stabilities (different heat contents) of the individual butenes.

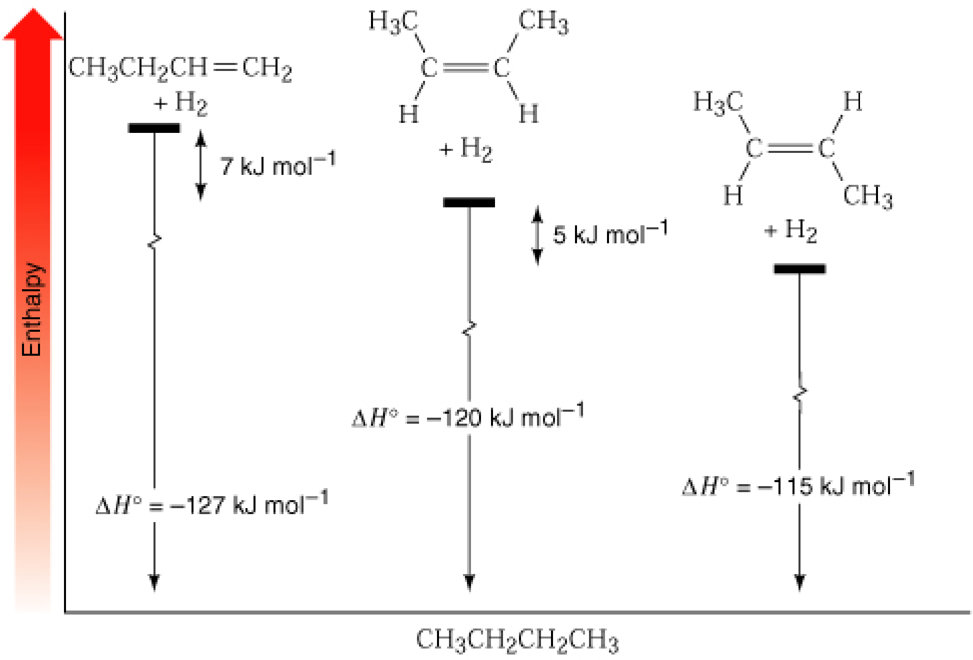


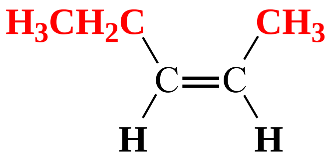
Figure 7.1 **An energy diagram for the three butene isomers. The order of stability is *trans*-2-butene > *cis*-2-butene > 1-butene.**

4) 1-Butene evolves the greatest amount of heat when hydrogenated, and *trans*-2-butene evolves the least.

i) 1-Butene must have the greatest energy (enthalpy) and be the least stable isomer.

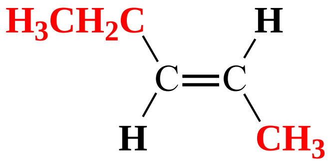
ii) *trans*-2-Butene must have the lowest energy (enthalpy) and be the most stable isomer.

3. Trend of stabilities: ***trans* isomer > *cis* isomer**



$$+ \ H_2 \xrightarrow{Pt} CH_3CH_2CH_2CH_2CH_3 \quad \Delta H^o = -120 \text{ kJ mol}^{-1}$$

***cis*-3-Pentene** **Pentane**



$$+ \ H_2 \xrightarrow{Pt} CH_3CH_2CH_2CH_2CH_3 \quad \Delta H^o = -115 \text{ kJ mol}^{-1}$$

***trans*-3-Pentene** **Pentane**

4. The greater enthalpy of *cis* isomers can be attributed to strain caused by the crowding of two alkyl groups on the same side of the double bond.

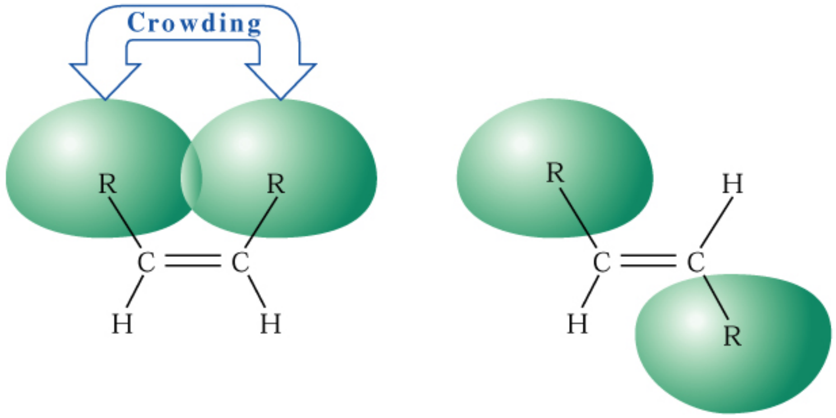


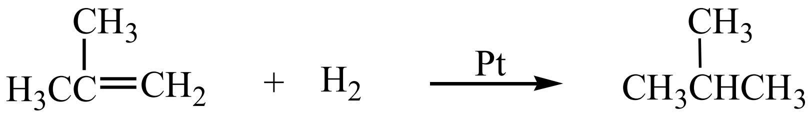
Figure 7.2 ***cis*- and *trans*-Alkene isomers. The less stable *cis* isomer has greater strain.**

7.3B RELATIVE STABILITIES FROM HEATS OF COMBUSTION

1. When hydrogenation os isomeric alkenes does not yield the same alkane, ***heats of***

combustion can be used to measure their relative stabilities.

1) 2-Methylpropene cannot be compared directly with other butene isomers.

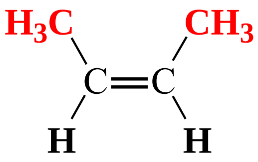


2-Methylpropene **Isobutane**

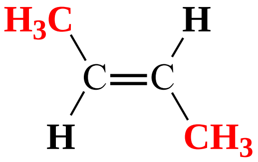
2) Isobutane and butane do not have the same enthalpy so a direct comparison of heats of hydrogenation is not possible.

2. 2-Methylpropene is the most stable of the four C_4H_8 isomers:

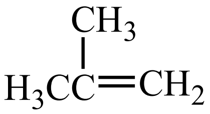
$$CH_3CH_2CH{=}CH_2 + 6\ O_2 \longrightarrow 4\ O_2 + 4\ H_2O \qquad \Delta H^o = -2719\ \text{kJ mol}^{-1}$$



$$+ 6\ O_2 \longrightarrow 4\ O_2 + 4\ H_2O \qquad \Delta H^o = -2712\ \text{kJ mol}^{-1}$$

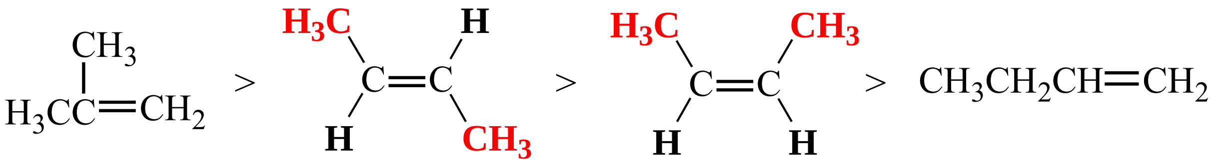


$$+ 6\ O_2 \longrightarrow 4\ O_2 + 4\ H_2O \qquad \Delta H^o = -2707\ \text{kJ mol}^{-1}$$



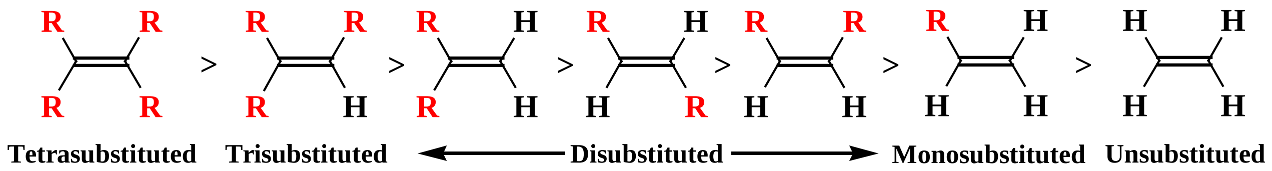
$$+ 6\ O_2 \longrightarrow 4\ O_2 + 4\ H_2O \qquad \Delta H^o = -2703\ \text{kJ mol}^{-1}$$

3. The stability of the butene isomers:



7.3C OVERALL RELATIVE STABILITIES OF ALKENES

1. **The greater the number of attached alkyl groups (i.e., the more substituted the carbon atoms of the double bond), the greater is the alkene's stability**.



7.4 CYCLOALKENES

1. The rings of cycloalkenes containing five carbon atoms or fewer exist only in the *cis* form.

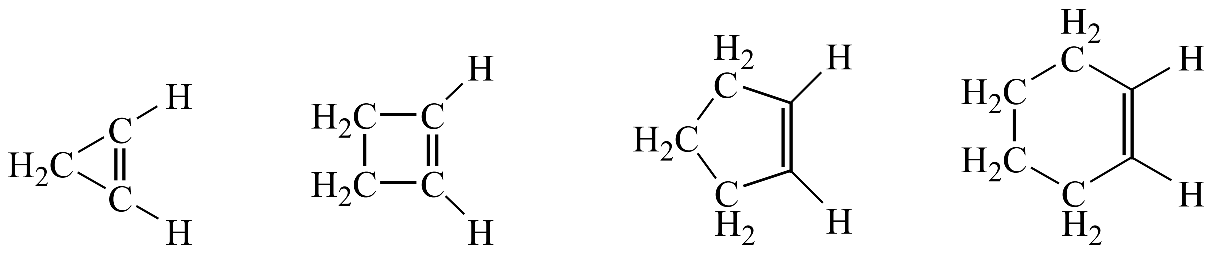


Figure 7.3 ***cis*-Cycloalkanes.**

2. There is evidence that *trans*-cyclohexene can be formed as a very reactive short-lived intermediate in some chemical reactions.

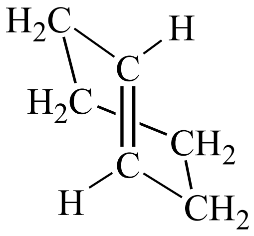


Figure 7.4 **Hypothetical *trans*-cyclohexene. This molecule is apparently too highly strained to exist at room temperature.**

3. *trans*-Cycloheptene has been observed spectroscopically, but it is a substance with very short lifetime and has not been isolated.

4. *trans*-Cyclooctene has been isolated.
   1) The ring of *trans*-cyclooctene is large enough to accommodate the geometry required by trans double bond and still be stable at room temperature.

2) *trans*-Cyclooctene is chiral and exists as a pair of enantiomers.

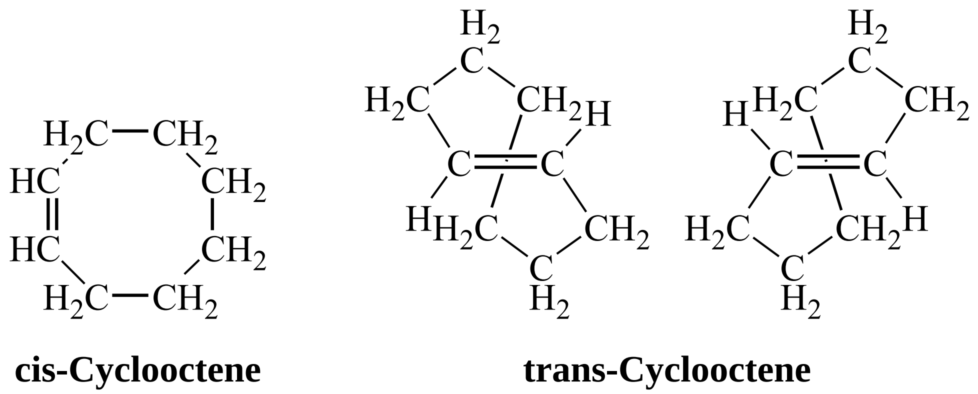
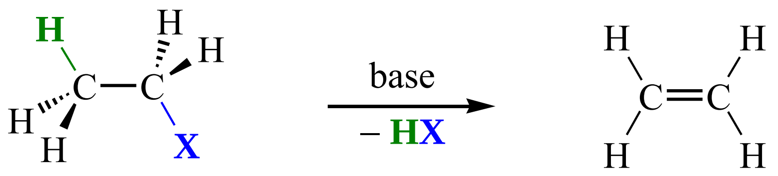


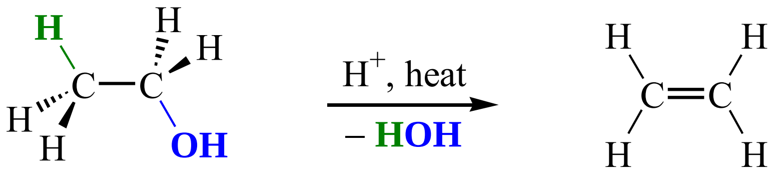
Figure 7.5 **The *cis*- and *trans* forms of cyclooctene.**

7.5 SYNTHESIS OF ALKENES VIA ELIMINATION REACTIONS

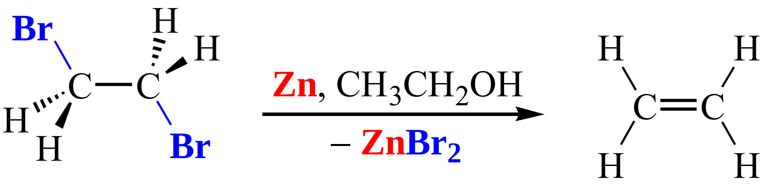
1. **Dehydrohalogenation of Alkyl Halides**



2. **Dehydration of Alcohols**

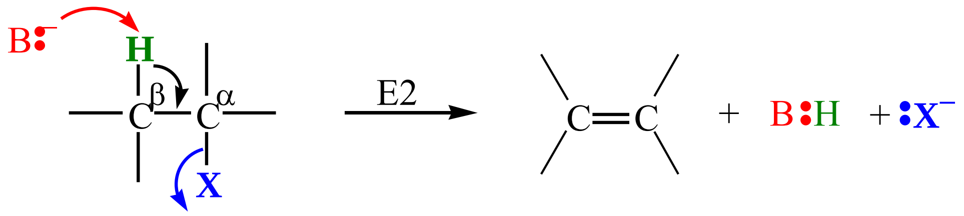


3. **Debromination of *vic*-Dibromides**



7.6 DEHYDROHALOGENATION OF ALKYL HALIDES

1. Synthesis of an alkene by dehydrohalogenation is almost always better achieved by an E2 reaction:

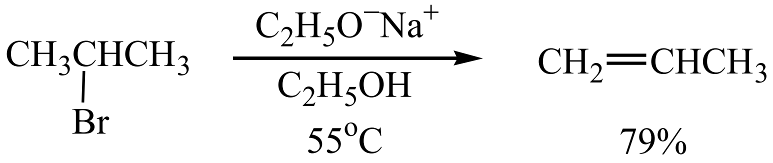


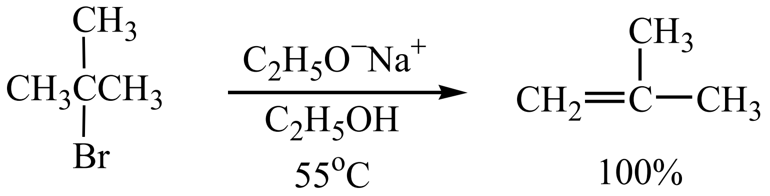
2. A secondary or tertiary alkyl halide is used if possible in order to bring about an E2 reaction.
3. A high concentration of a strong, relatively nonpolarizable base, such alkoxide ion, is used to avoid E1 reaction.
4. A relatively polar solvent such as an alcohol is employed.
5. To favor elimination generally, a relatively high temperature is used.
6. Sodium ethoxide in ethanol and potassium *tert*-butoxide in *tert*-butyl alcohol are typical reagents.
7. Potassium hydroxide in ethanol is used sometimes:

$$OH^- + C_2H_5OH \rightleftharpoons H_2O + C_2H_5O^-$$

7.6A E2 REACTIONS: THE ORIENTATION OF THE DOUBLE BOND IN THE PRODUCT ZAITSEV'S RULE

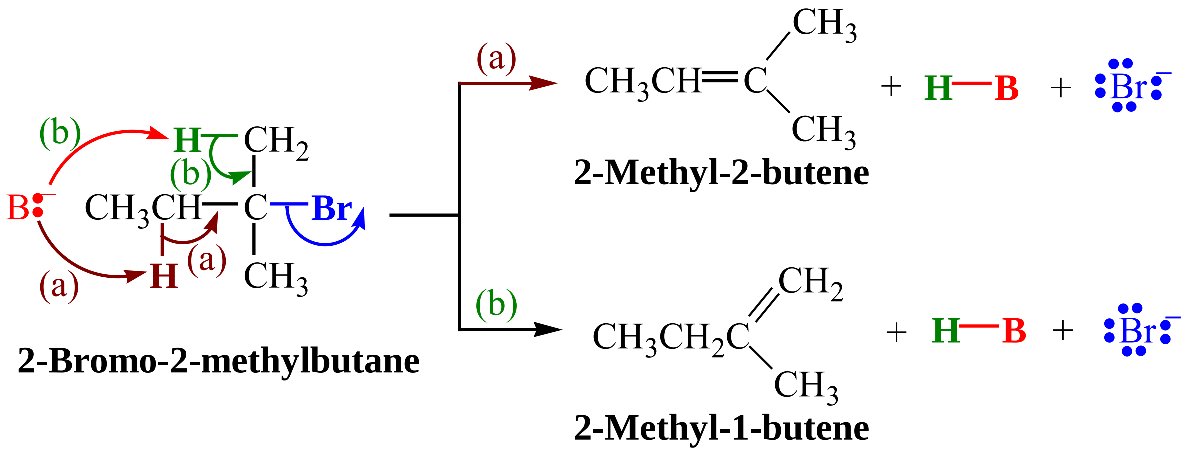
1. For some dehydrohalogenation reactions, a single elimination product is possible:.



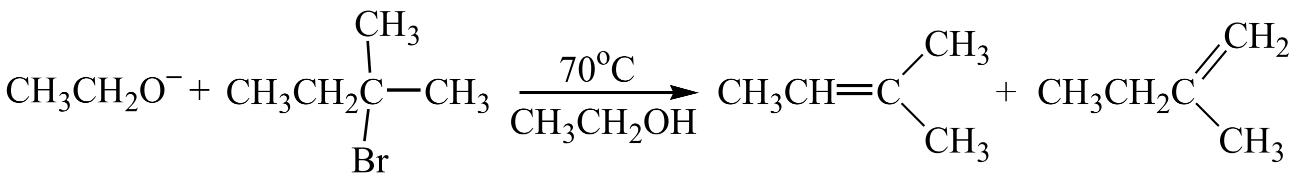


$$CH_3(CH_2)_{15}CH_2CH_2Br \xrightarrow[(CH_3)_3COH,\ 40^{o}C]{(CH_3)_3CO^{-}K^{+}} CH_3(CH_2)_{15}CH{=}CH_2 \quad 85\%$$

2. Dehydrohalogenation of many alkyl halides yields more than one product:



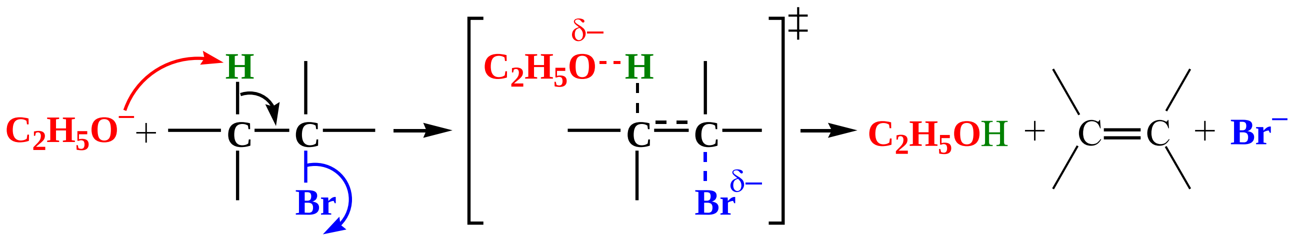
1) When a small base such as ethoxide ion or hydroxide ion is used, the major product of the reaction will be **the more stable alkene**.



2-Methyl-2-butene (69%) (**more stable**) **2-Methyl-1-butene** (31%) (**less stable**)

i) The more stable alkene has the more highly substituted double bond.

2. The transition state for the reaction:



Transition state for an E2 reaction
The carbon-carbon bond has some
of the character of a double bond.

1) The transition state for the reaction leading to 2-methyl-2-butene has the

developing character of a double bond in a **trisubstituted** alkene.

2) The transition state for the reaction leading to 2-methyl-1-butene has the developing character of a double bond in a **disubstituted** alkene.

3) Because the transition state leading to 2-methyl-2-butene resembles a more stable alkene, this transition state is more stable.

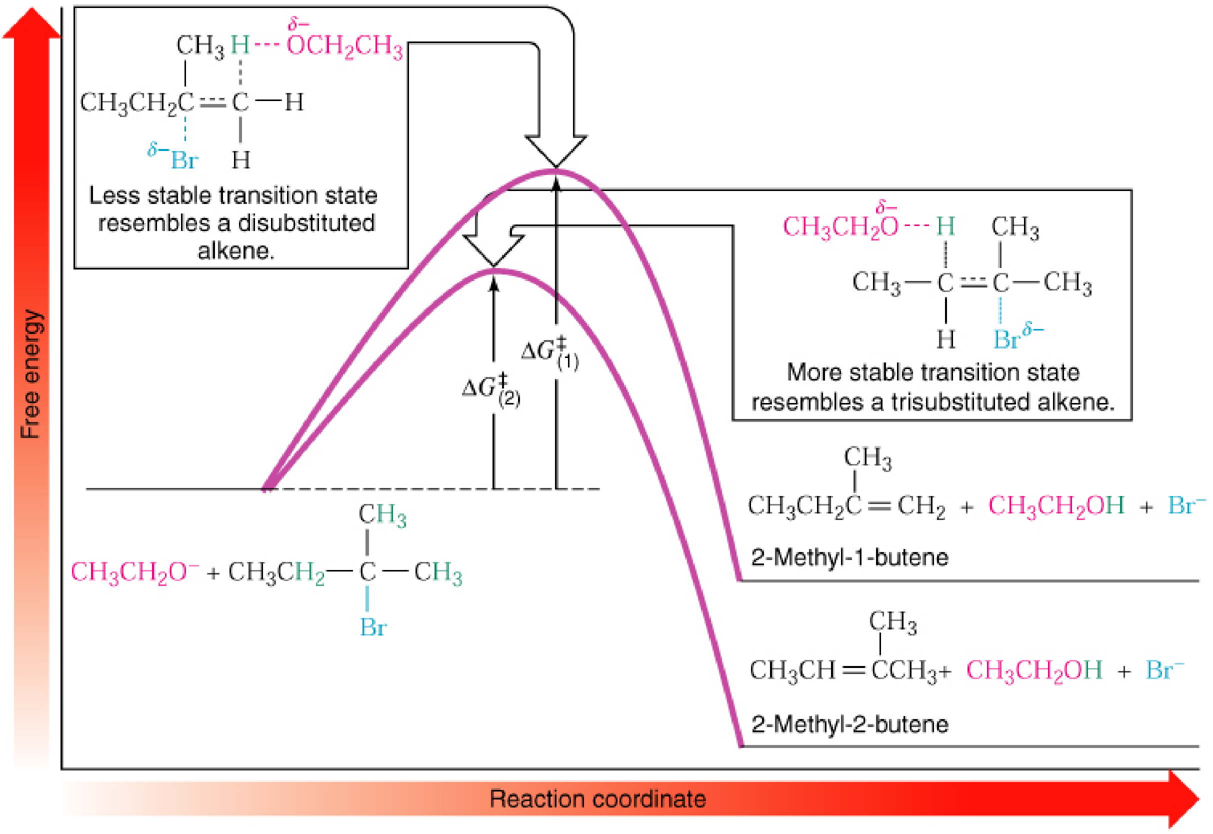


Figure 7.6 **Reaction (2) leading to the the more stable alkene occurs faster than reaction (1) leading to the less stable alkene; $\Delta G^{\ddagger}_{(2)}$ is less than $\Delta G^{\ddagger}_{(1)}$.**

i) Because this transition state is more stable (occurs at lower free energy), the free energy of activation for this reaction is lower and 2-methyl-2-butene is formed faster.

4) These reactions are known to be under kinetic control.

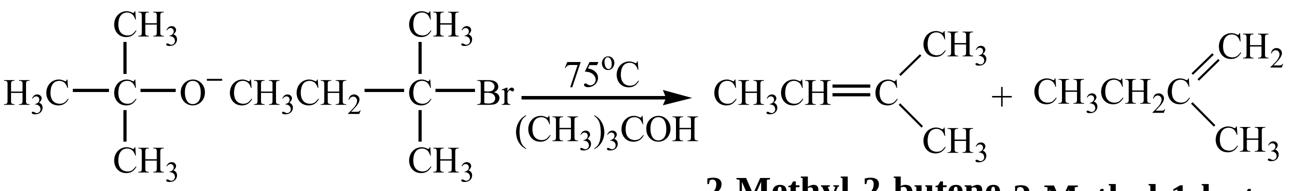
3. **Zaitsev rule:** an elimination occurs to give the most stable, more highly substituted alkene

1) Russian chemist A. N. Zaitsev (1841-1910).

2) Zaitsev's name is also transliterated as Zaitzev, Saytzeff, or Saytzev.

7.6B AN EXCEPTION TO ZAITSEV'S RULE

1. A bulky base such as potassium *tert*-butoxide in *tert*-butyl alcohol favors the formation of **the less substituted alkene** in dehydrohalgenation reactions.



2-Methyl-2-butene (27.5%) (**more substituted**)   **2-Methyl-1-butene** (72.5%) (**less substituted**)

1) The reason for leading to **Hofmann's** product:

i) The steric bulk of the base.

ii) The association of the base with the solvent molecules make it even larger.

iii) *tert*-Butoxide removes one of the more exposed (1°) hydrogen atoms instead of the internal (2°) hydrogen atoms due to its greater crowding in the transition state.

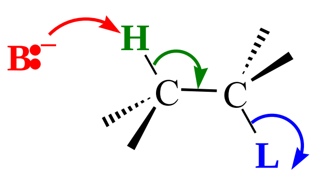
7.6C THE STEREOCHEMISTRY OF E2 REACTIONS: THE ORIENTATION OF GROUPS IN THE TRANSITION STATE

1. **Periplannar:**

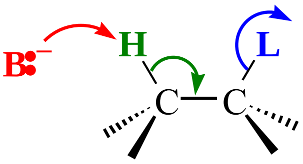
1) The requirement for coplanarity of the H–C–C–L unit arises from a need for proper overlap of orbitals in the developing π bond of the alkene that is being formed.

2) **Anti periplannar conformation:**

i) The anti periplannar transition state is staggered (and therefore of lower energy) and thus is the preferred one.



Anti periplanar transition state (preferred)

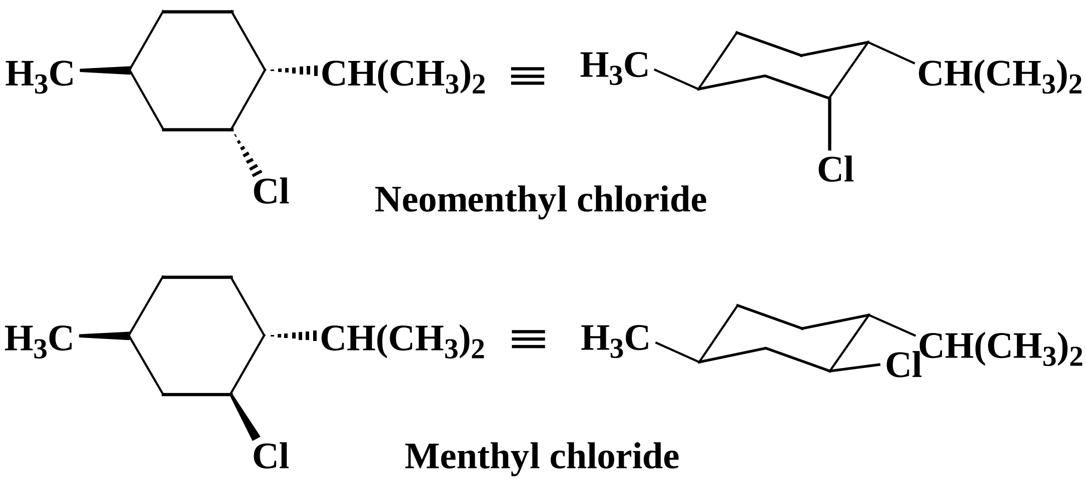


Syn periplanar transition state (only with certain rigid molecules)

3) **Syn periplannar conformation:**

   i) The syn periplannar transition state is eclipsed and occurs only with rigid molecules that are unable to assume the anti arrangement.

2. **Neomenthyl chloride and menthyl chloride:**



1) The β-hydrogen and the leaving group on a cyclohexane ring can assume an anti periplannar conformation **only when they are both axial:**

Here the β-hydrogen and the chlorine are both axial. This allow an antiperiplanar transition state.

A Newman projection formula shows that the β-hydrogen and the chlorine are anti periplanar when they are both axial.

2) **The more stable conformation of neomenthyl chloride:**

   i) The alkyl groups are both equatorial and the chlorine is **axial**.

   ii) There also **axial hydrogen atoms** on both C1 and C3.

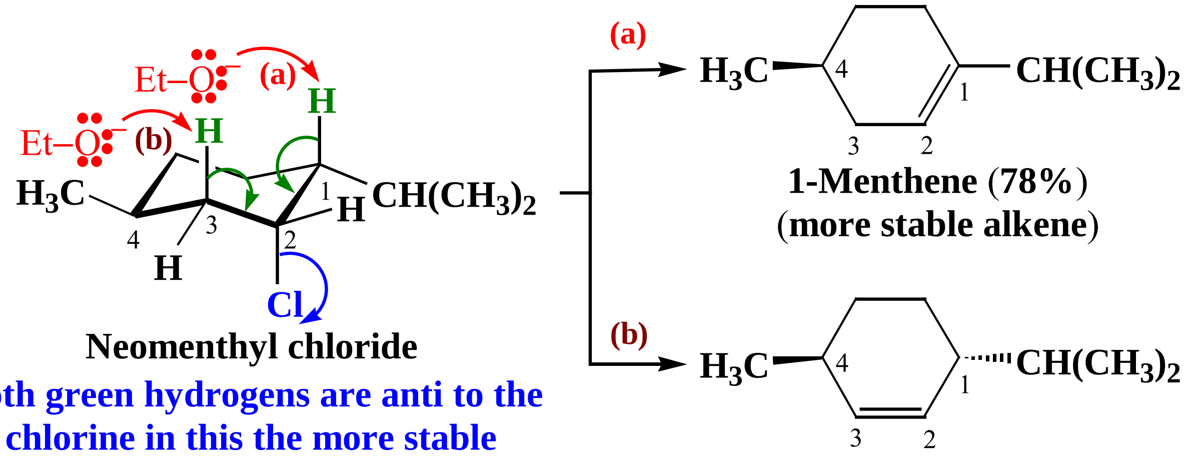
ii) The **base** can attack either of these hydrogen atoms and achieve an anti periplannar transition state for an E2 reaction.

ii) Products corresponding to each of these transition states (2-menthene and 1-menthene) are formed rapidly.

v) 1-Menthene (with the more highly substituted double bond) is the major product (**Zaitsev's rule**).

A Mechanism for the Elimination Reaction of Neomenthyl Chloride

E2 Elimination Where There Are Two Axial Cyclohexane β-Hydrogens



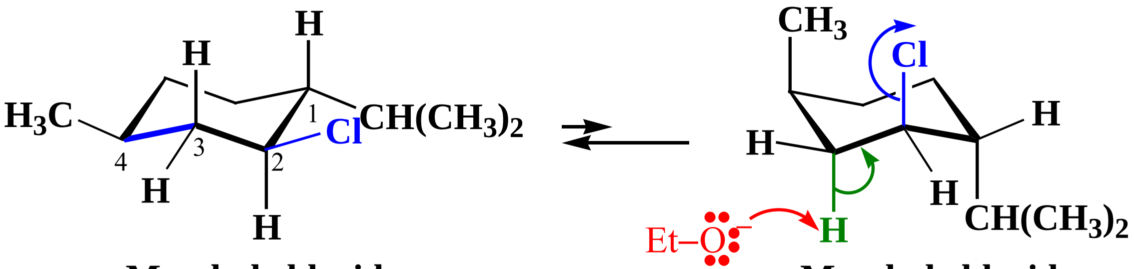
Neomenthyl chloride

Both green hydrogens are anti to the chlorine in this the more stable conformatio. Elimination by path (a) leads to 1-menthene; by path (b) to 2-menthene.

2-Menthene (22%)
(**less stable alkene**)

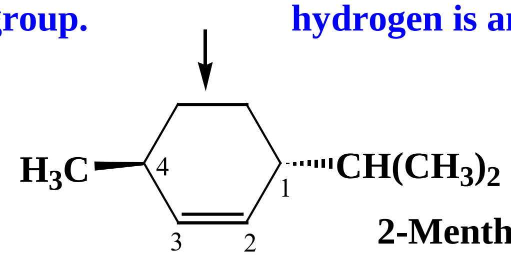
A Mechanism for the Elimination Reaction of Menthyl Chloride

E2 Elimination Where The Only Eligible Axial Cyclohexane β-Hydrogen is From a Less Stable Conformer



Menthyl chloride
(***more stable conformation***)
Elimination is not possible for this conformation because no hydrogen is anti to the leaving group.

Menthyl chloride
(***less stable conformation***)
Elimination is possible for this conformation because the green hydrogen is anti to the chlorine.



2-Menthene (**100%**)

3) **The more stable conformation of menthyl chloride:**

i) The alkyl groups and the chlorine are **equatorial**.

ii) For the chlorine to become **axial**, menthyl chloride has to assume a conformation in which the large isopropyl group and the methyl group are also **axial**.

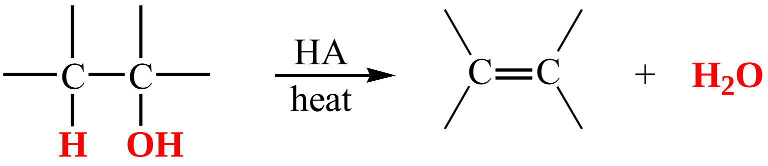
ii) This conformation is of much higher energy, and the free energy of activation for the reaction is large because it includes the energy necessary for the conformational change.

ii) Menthyl chloride undergoes an E2 reaction very slowly, and the product is entirely 2-menthene (**Hofmann product**).

7.7 DEHYDRATION OF ALCOHOLS

1. **Dehydration of alcohols:**

1) Heating most alcohols with a strong acid causes them to lose a molecule of water and form an alkene:



2. The reaction is an **elimination** and is favored at higher temperatures.

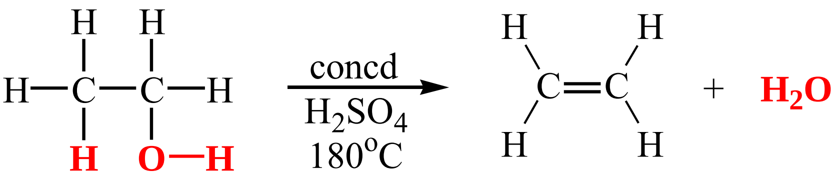
1) The most commonly used acids in the laboratory are Brønsted acids —— proton donors such as sulfuric acid and phosphoric acid.

2) Lewis acids such as alumina (Al_2O_3) are often used in industrial, fas phase dehydrations.

3. Characteristics of dehydration reactions:

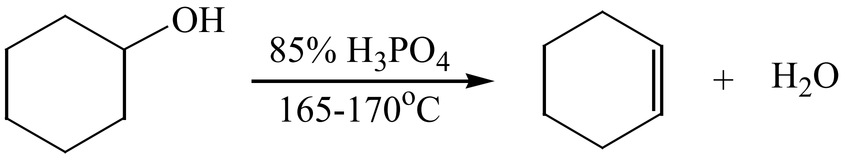
1) **The experimental conditions — temperature and acid concentration — that are required to bring about dehydration are closely related to the structure of the individual alcohol.**

i) Primary alcohols are the most difficult to dehydrate:



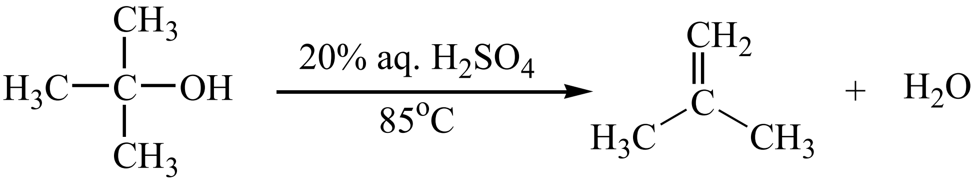
Ethanol (a 1° alcohol)

ii) Secondary alcohols usually dehydrate under milder conditions:



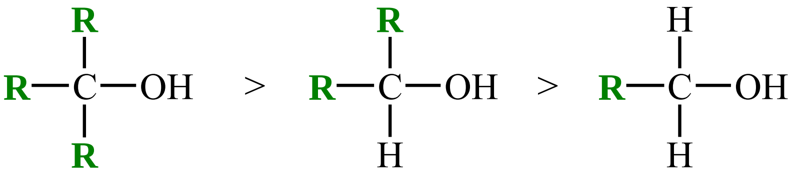
Cyclohexanol **Cyclohexene (80%)**

iii) Tertiary alcohols are usually dehydrated under extremely mild conditions:



***tert*-Butyl alcohol** **2-Methylpropene (84%)**

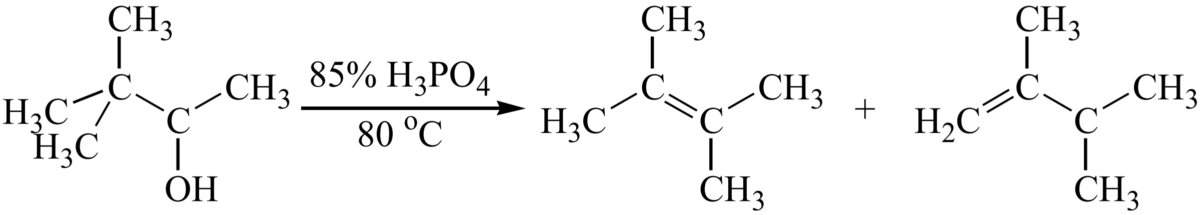
iv) Relative ease of order of dehydration of alcohols:



3° Alcohol **2° Alcohol** **1° Alcohol**

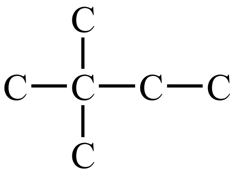
2) **Some primary and secondary alcohols also undergo rearrangements of their carbon skeleton during dehydration.**

i) Dehydration of 3,3-dimethyl-2-butanol:

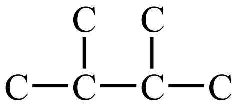


3,3-Dimethyl-2-butanol **2,3-Dimethyl-2-butene (80%)** **2,3-Dimethyl-1-butene (20%)**

ii) The carbon skeleton of the reactant is



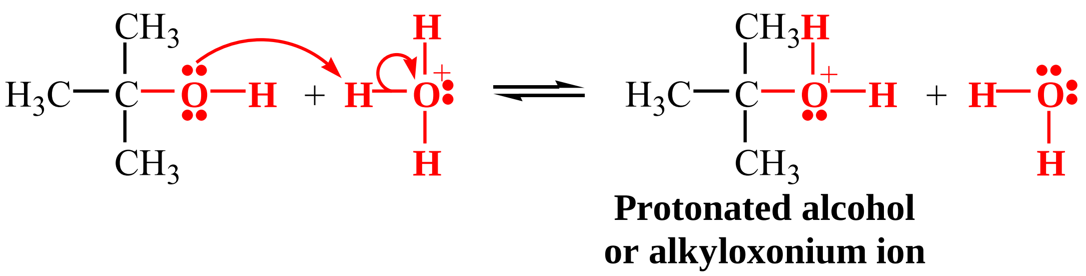
while that of the products is



7.7A MECHANISM OF ALCOHOL DEHYDRATION: AN E1 REACTION

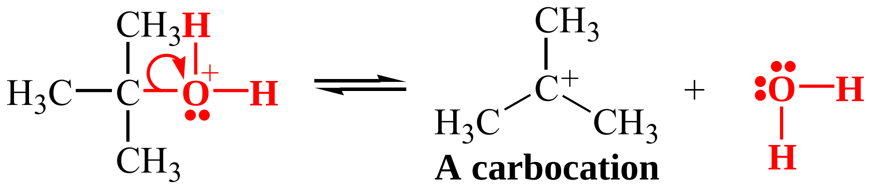
1. The mechanism is ***an E1 reaction in which the substrate is a protonated alcohol*** (***or an alkyloxonium ion***).

Step 1

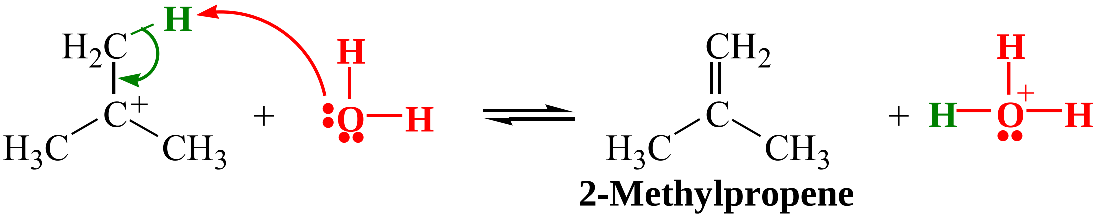


1) In step 2, the leaving group is a molecule of water.
2) The carbon-oxygen bond breaks **heterolytically**.
3) It is a highly **endergonic step** and therefore is the slowest step.

Step 2

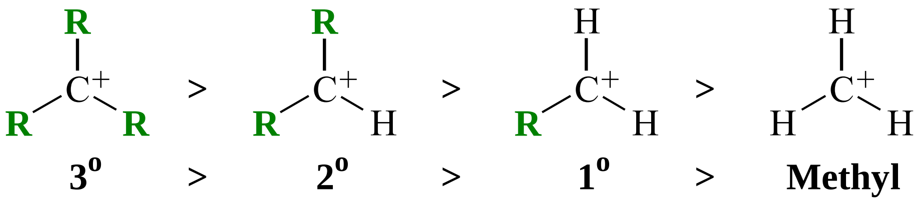


Step 3



7.7B CARBOCATION STABILITY AND THE TRANSITION STATE

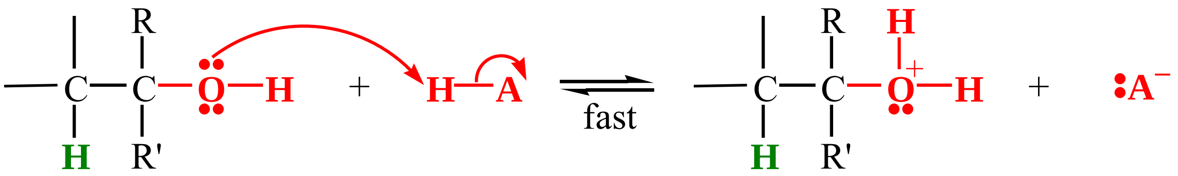
1. The order of stability of carbocations is 3° > 2° > 1° > methyl:



A Mechanism for the Reaction

Acid-Catalyzed Dehydration of Secondary or Tertiary Alcohols: An E1 Reaction

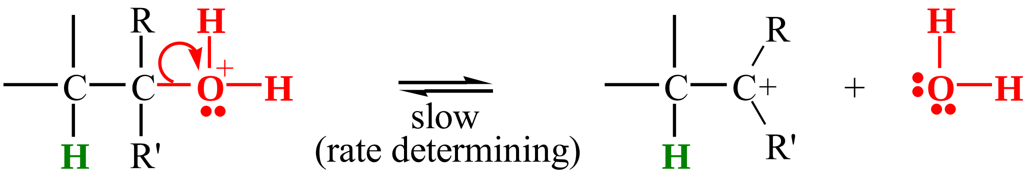
Step 1



2° or 3° Alcohol (R' may be H) **Strong acid (typically sulfuric or phosphoric acid)** **Protonated alcohol** **Conjugate base**

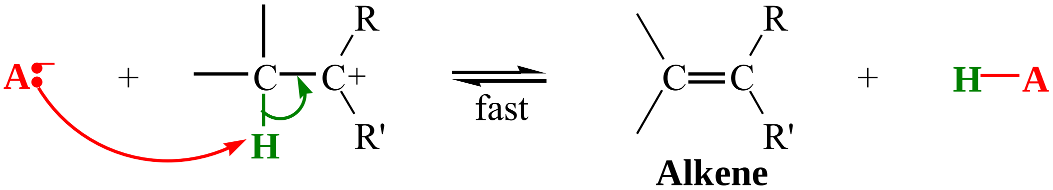
The alcohol accepts a proton from the acid in a fast step.

Step 2



The protonated alcohol loses a molecule of water to become a carbocation. This step is slow and rate determining

Step 3



Alkene

The carbocation loses a proton to a base. In this step, the base may be another molecule of the alcohol, water, or the conjugate base of the acid. The proton transfer results in the formation of the alkene. Note that the overall role of the acid is catalytic (it is used in the reaction and regenerated).

2. The order of free energy of activation for dehydration of alcohols is 3° > 2° > 1° > methyl:

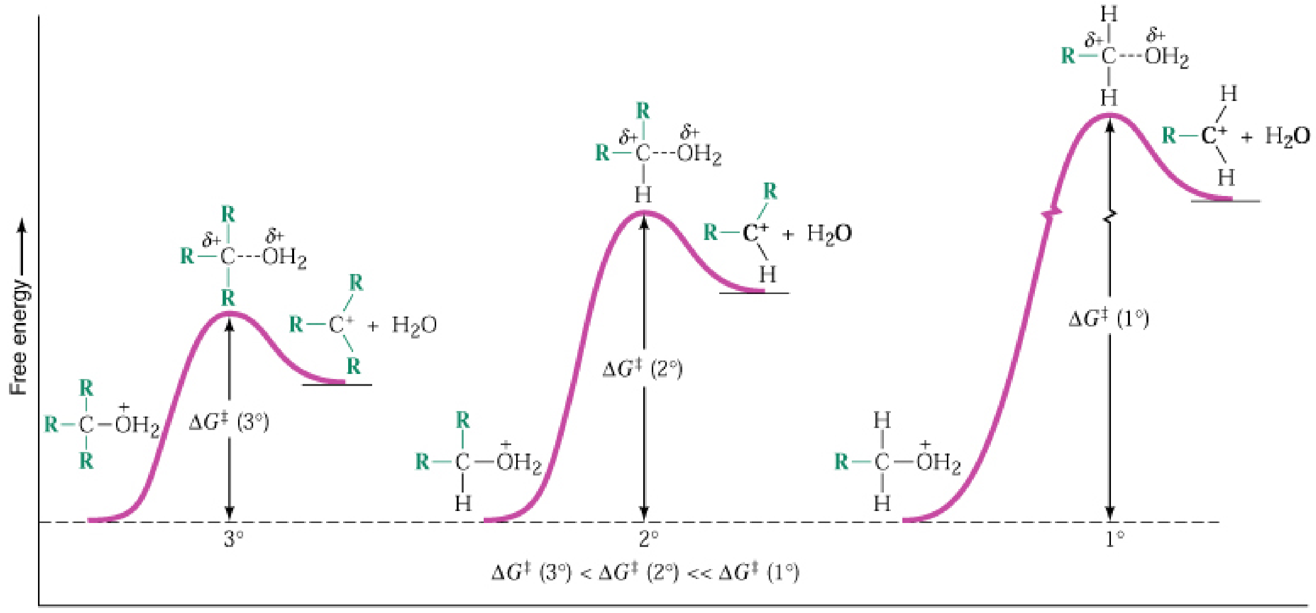
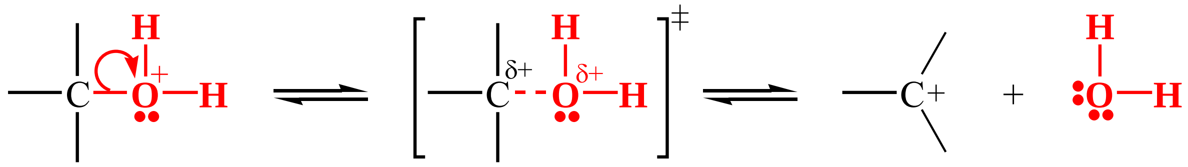


Figure 7.7 **Free-energy diagrams for the formation of carbocations from protonated tertiary, secondary, and primary alcohols. The relative free energies of activation are tertiary < secondary « primary.**

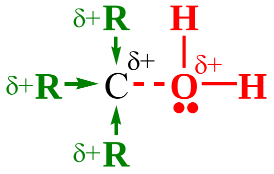
3. **Hammond-Leffler postulate:**

1) There is a strong resemblance between the transition state and the cation product.
2) **The transition state that leads to the 3° carbocation is lowest in free energy because it resembles the most stable product**.
3) **The transition state that leads to the 1° carbocation is highest in free energy because it resembles the least stable product**.

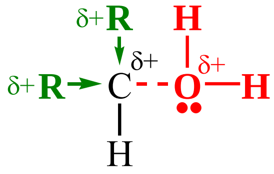
4. **Delocalization of the charge** stabilizes the transition state and the carbocation.



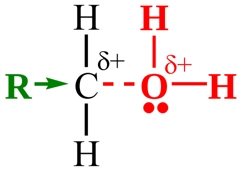
1) The carbon begins to develop a partial positive charge because it is losing the electrons that bonded it to the oxygen atom.
2) This developing positive charge ***is most effectively delocalized in the transition state leading to a 3° carbocation because of the presence of three electron-releasing alkyl groups***.



Transition state leading to 3° carbocation (most stable)



Transition state leading to 2° carbocation



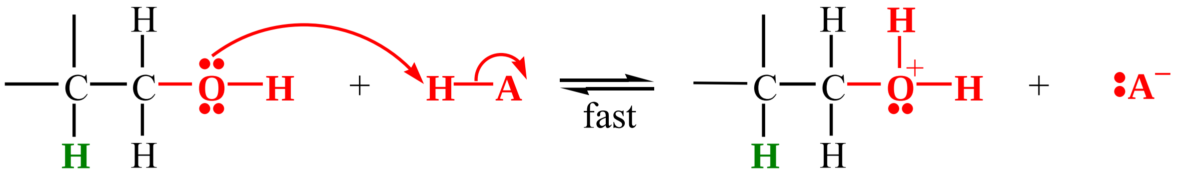
Transition state leading to 1° carbocation (least stable)

3) Because this developing positive charge is least effectively delocalized in the transition state leading to a 1° carbocation, the dehydration of a 1° alcohol proceeds through a different mechanism —— an E2 mechanism.

7.7C A Mechanism for Dehydration of Primary Alcohols: An E2 Reaction

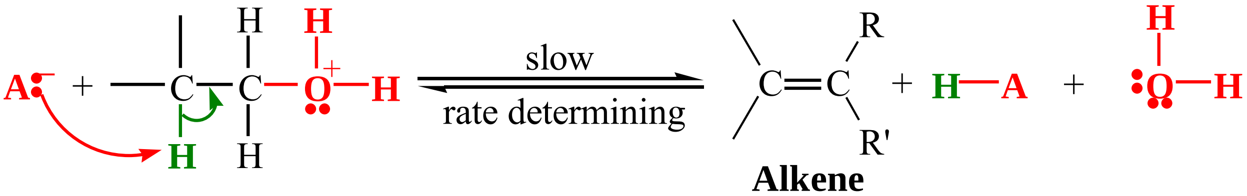
A Mechanism for the Reaction

Dehydration of a Primary Alcohol: An E2 Reaction



Primary alcohol **Strong acid (typically sulfuric or phosphoric acid)** **Protonated alcohol** **Conjugate base**

The alcohol accepts a proton from the acid in a fast step.



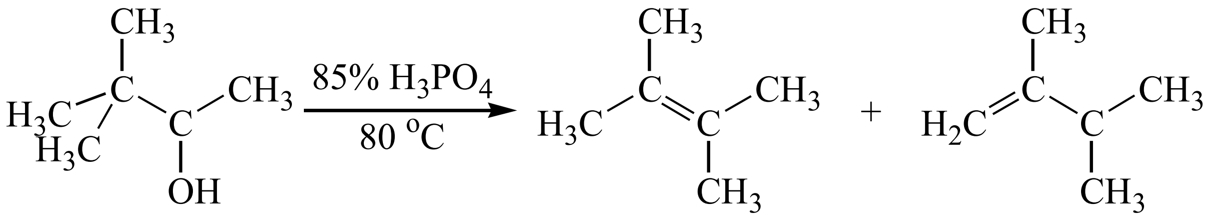
Alkene

A base removes a hydrogen from the β carbon as the double bond forms and the protonated hydroxyl group departs. (The base may be another molecule of the alcohol or the conjugate base of the acid)

7.8 Carbocation Stability and the Occurrence of

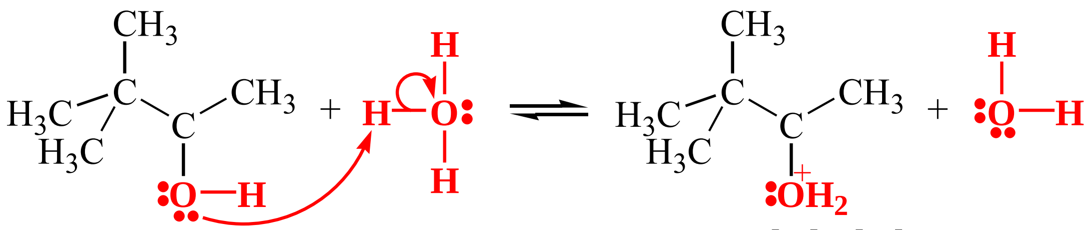
Molecular Rearrangements

7.8A Rearrangements During Dehydration of Secondary Alcohols



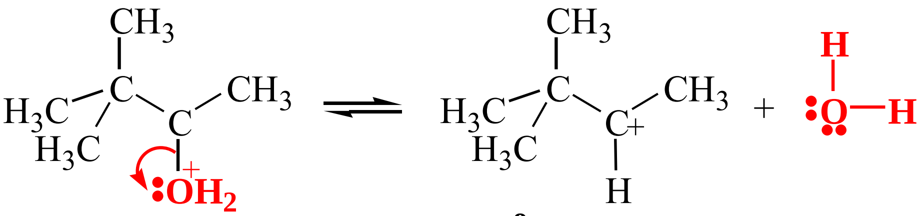
3,3-Dimethyl-2-butanol **2,3-Dimethyl-2-butene (major product)** **2,3-Dimethyl-1-butene (minor product)**

Step 1



Protonated alcohol

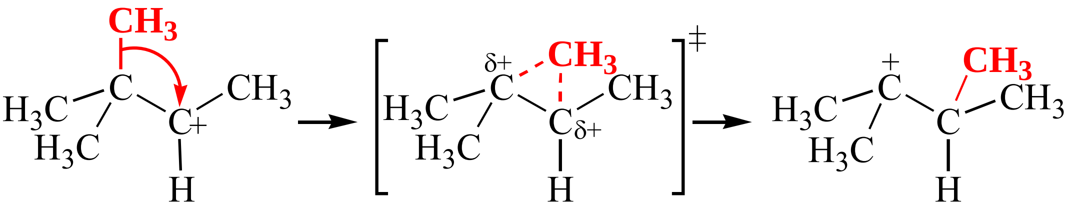
Step 2



A 2° carbocation

1. **The less stable, 2° carbocation rearranges to a more stable 3° carbocation**.

Step 3



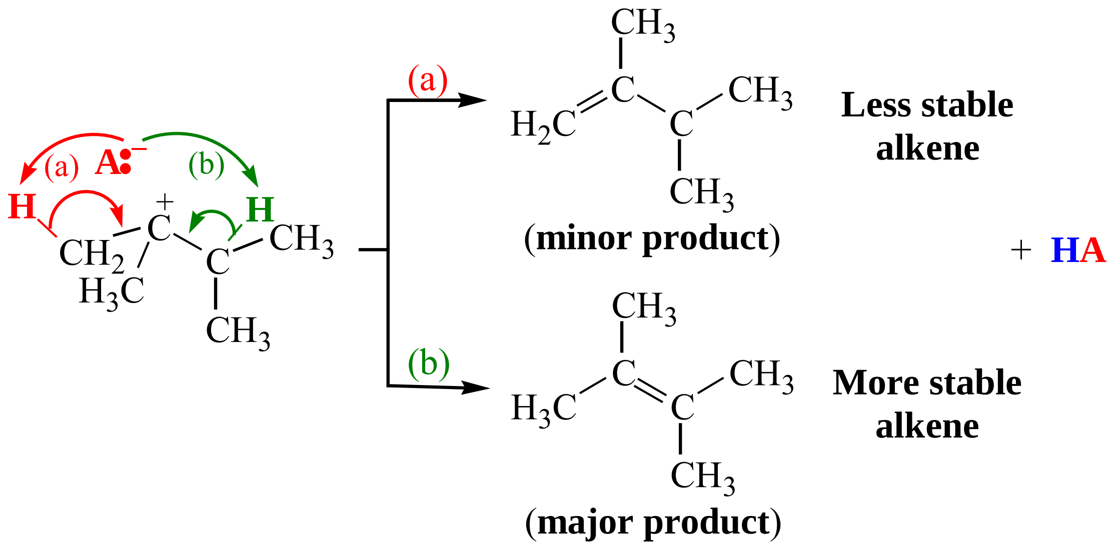
A 2° carbocation (less stable) **Transition state** **A 3° carbocation (more stable)**

2. The methyl group migrates **with its pair of electrons**, as a methyl anion, $^{-}$**:**CH_3 (a **methanide** ion).
3. **1,2-Shift:**
4. In the transition state the shifting methyl is partially bonded to both carbon atoms

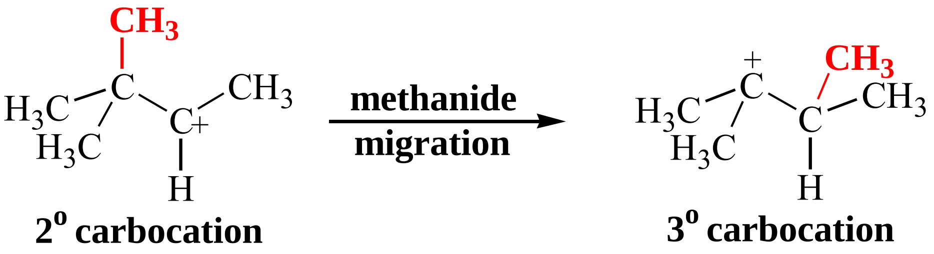
by the pair of electrons with which it migrates. It never leaves the carbon skeleton.

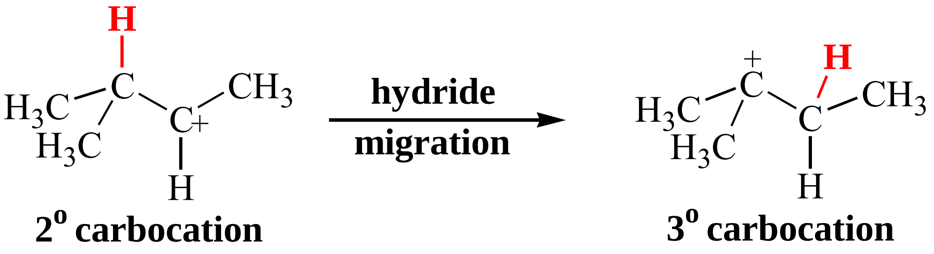
5. There two ways to remove a proton from the carbocation:
   1) Path (b) leads to the highly stable tetrasubstituted alkene, and this is the path followed by most of the carbocations.
   2) Path (a) leads to a less stable, disubstituted alkene and produces the minor product of the reaction.
   3) ***The formation of the more stable alkene is the general rule (Zaitsev's rule) in the acid-catalyzed dehydration reactions of alcohols***.

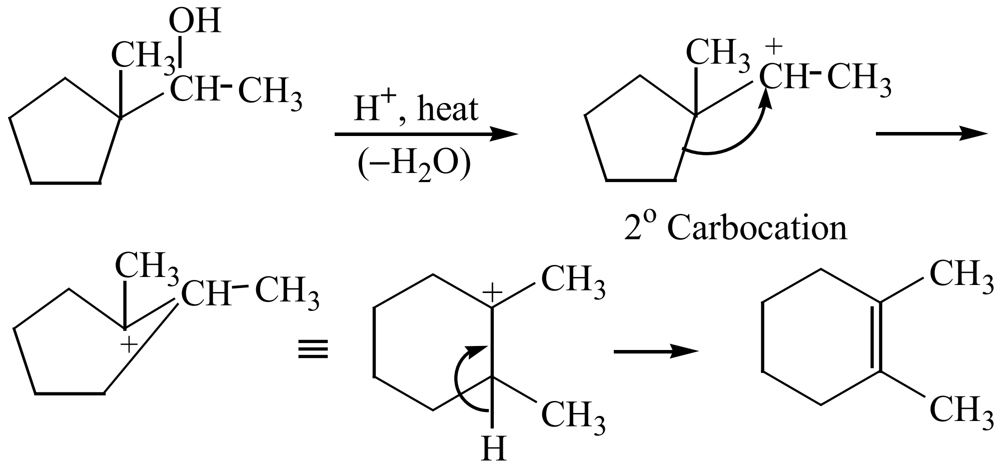
Step 4



6. **Rearrangements occur almost invariably when the migration of an alkanide ion or hydride ion can lead to a more stable carbocation**.







7.8B REARRANGEMENTS AFTER DEHYDRATION OF A PRIMARY ALCOHOL

1. The alkene that is formed initially from a 1° alcohol arises by an E2 mechanism.

   1) An alkene can accept a proton to ***generate*** a carbocation in a process that is essentially the reverse of the ***deprotonation*** step in the E1 mechanism for dehydration of an alcohol.

   2) When a terminal alkene protonates by using its π electrons to bond a proton at the terminal carbon, a carbocation forms at the second carbon of the chain (The carbocation could also form directly from the 1° alcohol by a hydride shift from its β-carbon to the terminal carbon as the protonated hydroxyl group departs).

   3) Various processes can occur from this carbocation:

      i) A different β-hydrogen may be removed, leading to a more stable alkene than the initially formed terminal alkene.

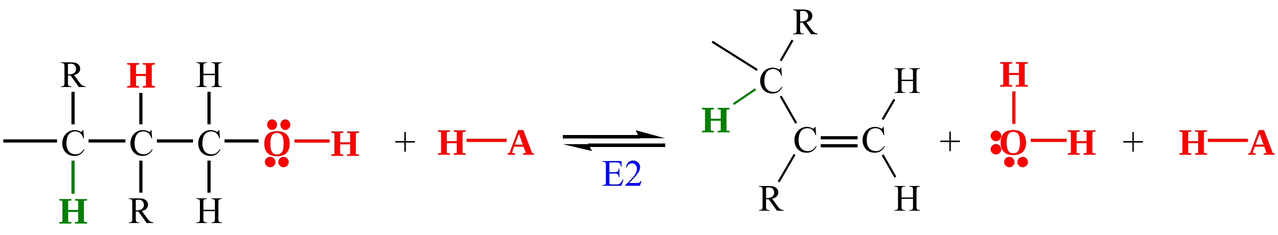
      ii) A hydride or alkanide rearrangement may occur leading to a more stable carbocation, after which elimination may be completed.

      iii) A nucleophile may attack any of these carbocations to form a substitution product.

      v) Under the high-temperature conditions for alcohol dehydration the principal products will be alkenes rather than substitution products.

A Mechanism for the Reaction

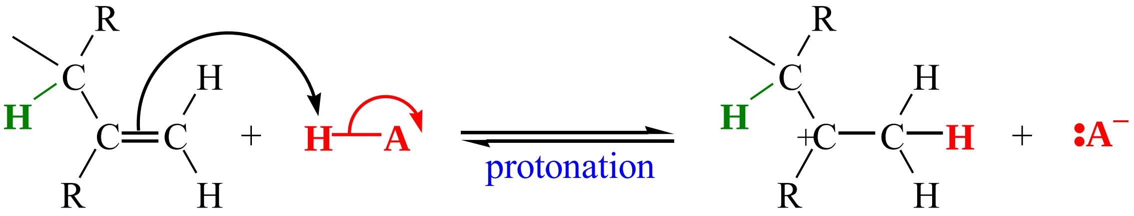
Formation of a Rearranged Alkene During Dehydration of a Primary Alcohol



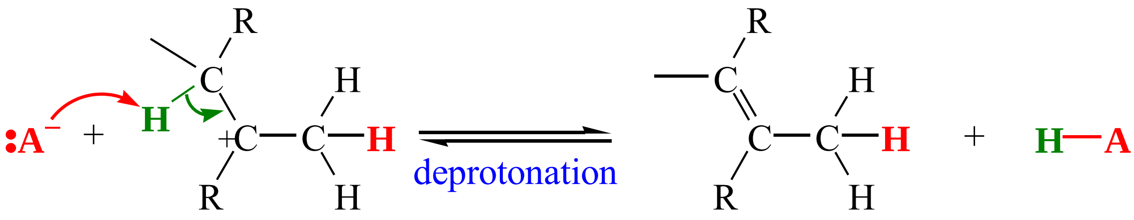
Primary alcohol (R may be H)

The initial alkene

The primary alcohol initially undergoes acid-catalyzed dehydration by an E2 mechanism



The π electrons of the initial alkene can then be used to form a bond with a proton at the terminal carbon, forming a secondary or tertiary carbocation.

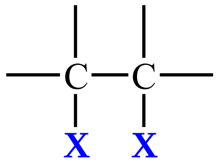


Final alkene

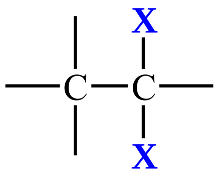
A different β-hydrogen can be removed from the carbocation, so as to form a more highly substituted alkene than the initial alkene. This deprotonation step is the same as the usual completion of an E1 elimination. (This carbocation could experience other fates, such as further rearrangement before elimination or substitution by an S_N1 process.)

7.9 ALKENES BY DEBROMINATION OF VICINAL DIBROMIDES

1. **Vicinal** (or ***vic***) and **geminal** (or ***gem***) dihalides:

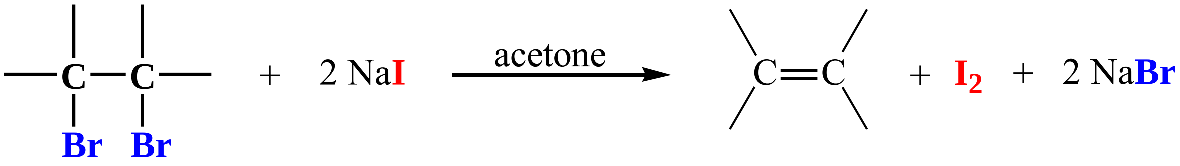


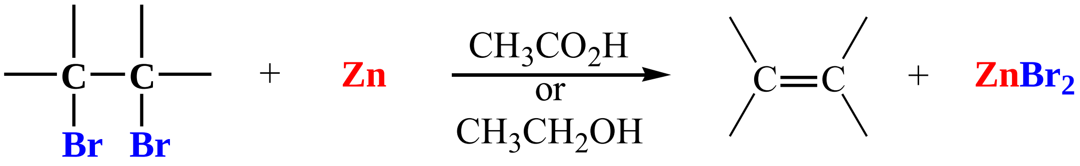
A *vic*-dihalide



A *gem*-dihalide

1) *vic*-Dibromides undergo **debromination**:

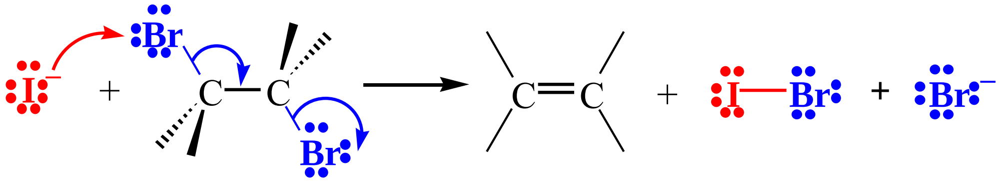




A Mechanism for the Reaction

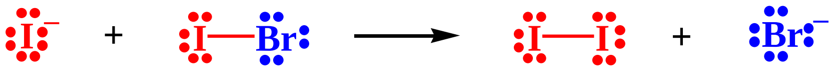
Mechanism:

Step 1



An iodide ion become bonded to a bromine atom in a step that is, in effect, an S_N2 attack on the bromine; removal of the bromine brings about an E2 elimination and the formation of a bouble bond.

Step 2



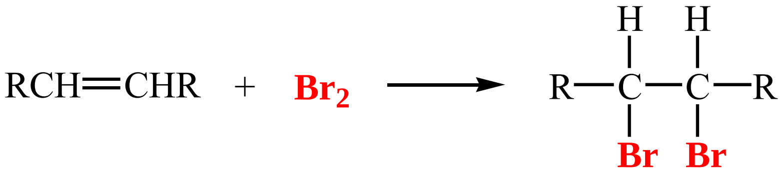
Here, an S_N2-type attack by iodide ion on IBr leads to the formation of I_2 and a bromide ion.

1. Debromination by zinc takes place on the surface of the metal and the mechanism is uncertain.
   1) Other electropositive metals (e.g., Na, Ca, and Mg) also cause debromination of *vic*-dibromide.

2. *vic*-Debromination are usually prepared by the addition of bromine to an alkene.
3. Bromination followed by debromination is useful in the purification of alkenes and in "protecting" the double bond.

7.10 SYNTHESIS OF ALKYNES BY ELIMINATION REACTIONS

1. Alkynes can be synthesized from alkenes.



***vic*-Dibromide**

   1) The *vic*-dibromide is dehydrohalogenated through its reaction with a strong base.
   2) The dehydrohalogenation occurs in two steps. Depending on conditions, these two dehydrohalogenations may be carried out as separate reactions, or they may be carried out consecutively in a single mixture.
      i) The strong base, $NaNH_2$, is capable of effecting both dehydrohalogenations in a single reaction mixture.
      ii) At least two molar equivalents of $NaNH_2$ per mole of the dihalide must be used, and if the product is a terminal alkyne, three molar equivalents must be used because the terminal alkyne is deprotonated by $NaNH_2$ as it is formed in the mixture.
      iii) Dehydrohalogenations with $NaNH_2$ are usually carried out in liquid ammonia or in an inert medium such as mineral oil.

A Mechanism for the Reaction

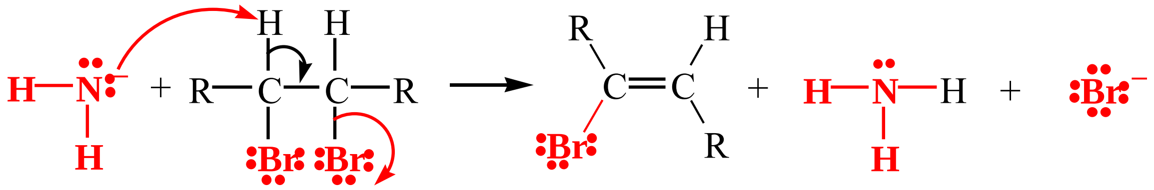
Dehydrohalogenation of *vic*-Dibromides to form Alkynes

Reaction:

$$RCH(Br)-CH(Br)R + 2\ NH_2^- \longrightarrow RC{\equiv}CR + 2\ NH_3 + 2\ Br^-$$

Mechanism:

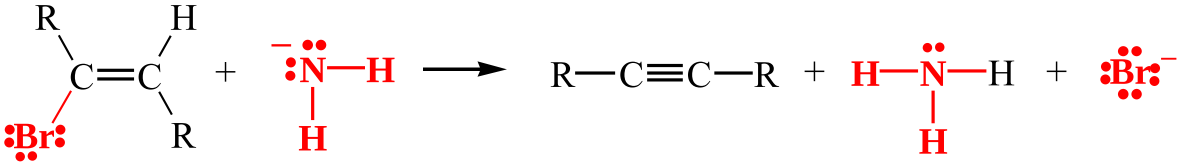
Step 1



Amide ion **vic-Dibromide** **Bromoalkene** **Ammonia** **Bromide ion**

The strongly basic amide ion brings about an E2 reaction.

Step 2



Bromoalkene **Amide ion** **Alkyne** **Ammonia** **Bromide ion**

A second E2 reaction produces the alkyne.

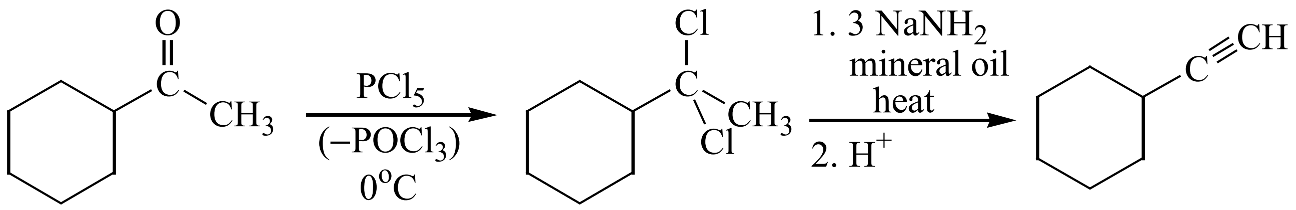
2. Examples:

$$CH_3CH_2CH{=}CH_2 \xrightarrow[CCl_4]{Br_2} CH_3CH_2CH(Br)CH_2Br \xrightarrow[\text{mineral oil, } 110\text{-}160\ ^oC]{NaNH_2}$$

$$\left[\begin{array}{c} CH_3CH_2CH{=}CHBr \\ + \\ H_3CH_2CC(Br){=}CH_2 \end{array}\right] \xrightarrow[\text{mineral oil, } 110\text{-}160\ ^oC]{NaNH_2} \left[H_3CH_2CC{\equiv}CH\right] \xrightarrow{NaNH_2}$$

$$H_3CH_2CC{\equiv}C{:}^-Na^+ \xrightarrow{NH_4Cl} H_3CH_2CC{\equiv}CH + NH_3 + NaCl$$

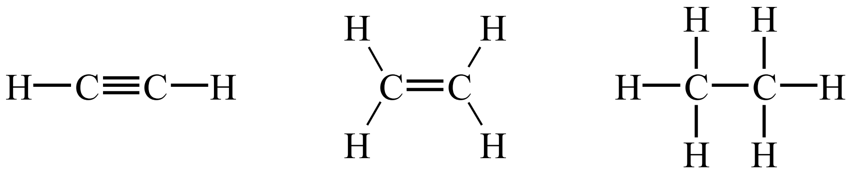
3. Ketones can be converted to *gem*-dichloride through their reaction with phosphorus pentachloride which can be used to synthesize alkynes.



Cyclohexyl methyl ketone | **A *gem*-dichloride (70-80%)** | **Cyclohexylene (46%)**

7.11 THE ACIDITY OF TERMINAL ALKYNES

1. The hydrogen atoms of ethyne are considerably more acidic than those of ethane or ethane:



pK_a = 25 | **pK_a = 44** | **pK_a = 50**

1) The order of basicities of anions is opposite that of the relative acidities of the hydrocarbons.

Relative Basicity of **ethanide**, **ethenide**, and **ethynide** ions:

$$CH_3CH_2\text{:}^- \;>\; CH_2\text{=}CH\text{:}^- \;>\; HC\equiv C\text{:}^-$$

Relative Acidity of hydrogen compounds of the first-row elements of the periodic table:

$$\text{H–OH} > \text{H–OR} > \text{H–C}\equiv\text{CR} > \text{H–NH}_2 > \text{H–CH=CH}_2 > \text{H–CH}_2\text{CH}_3$$

Relative Basicity of hydrogen compounds of the first-row elements of the periodic table:

$$^-\text{:OH} < {}^-\text{:OR} < {}^-\text{:C}\equiv\text{CR} < {}^-\text{:NH}_2 < {}^-\text{:CH=CH}_2 < {}^-\text{:CH}_2\text{CH}_3$$

2) **In solution**, terminal alkynes are more acidic than ammonia, however, they are less acidic than alcohols and are less acidic than water.

3) **In the gas phase**, the hydroxide ion is a stronger base than the acetylide ion.

   i) In solution, smaller ions (e.g., hydroxide ions) are more effectively solvated than larger ones (e.g., ethynide ions) and thus they are more stable and therefore less basic.

   ii) In the gas phase, large ions are stabilized by polarization of their bonding electrons, and the bigger a group is the more polarizable it will be and consequently larger ions are less basic

7.12 REPLACEMENT OF THE ACETYLENEIC HYDROGEN ATOM OF TERMINAL ALKYNES

1. Sodium alkynides can be prepared by treating terminal alkynes with $NaNH_2$ in liquid ammonia.

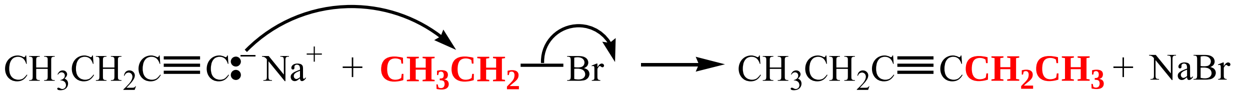
$$H–C≡C–H + NaNH_2 \xrightarrow{\text{liq. } NH_3} H–C≡C:^{-}\ Na^{+} + NH_3$$

$$CH_3C≡C–H + NaNH_2 \xrightarrow{\text{liq. } NH_3} CH_3C≡C:^{-}\ Na^{+} + NH_3$$

1) The amide ion (ammonia, pK_a = 38) is able to completely remove the acetylenic protons of terminal alkynes (pK_a = 25).

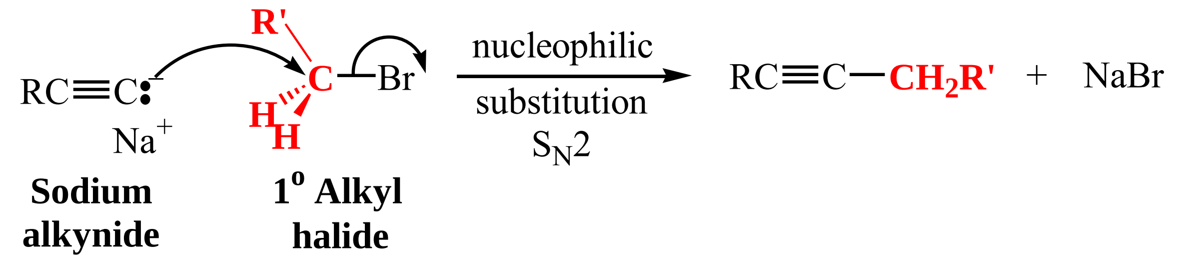
2. Sodium alkynides are useful intermediates for the synthesis of other alkynes.

Sodium alkynide **1° Alkyl halide** **Mono- or disubstituted acetylene**

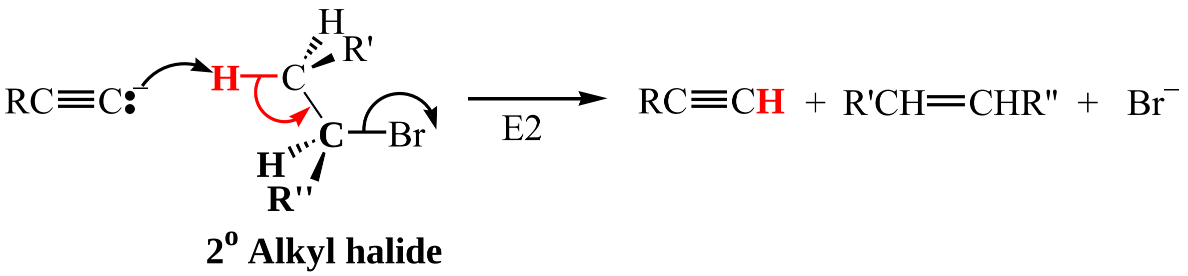


3-Hexyne (75%)

3. **An S_N2 reaction:**



4. This synthesis fails when secondary or tertiary halides are used because the alkynide ion acts as a base rather than as a nucleophile, and the major results is an **E2 elimination**.



7.13 HYDROGENATION OF ALKENES

1. **Catalytic hydrogenation (an addition reaction):**
   1) One atom of hydrogen ***adds*** to each carbon of the double bond.
   2) Without a catalyst the reaction does not take place at an appreciable rate.

$$CH_2{=}CH_2 + H_2 \xrightarrow[25\ ^{o}C]{\text{Ni, Pd or Pt}} CH_3{-}CH_3$$

$$CH_3CH{=}CH_2 + H_2 \xrightarrow[25\ ^{o}C]{\text{Ni, Pd or Pt}} CH_3CH_2{-}CH_3$$

2. **Saturated compounds:**
3. **Unsaturated compounds:**
4. The process of adding hydrogen to an alkene is a **reduction**.

7.14 HYDROGENATION: THE FUNCTION OF THE CATALYST

1. Hydrogenation of an alkene is an exothermic reaction ($\Delta H° \approx -120$ kJ mol^{-1}).

$$\text{R–CH=CH–R} + \text{H}_2 \xrightarrow{\text{hydrogenation}} \text{R–CH}_2\text{–CH}_2\text{–R} + \text{heat}$$

1) Hydrogenation reactions usually have high free energies of activation.
2) The reaction of an alkene with molecular hydrogen does not take place at room temperature in the absence of a catalyst, but it often ***does*** take place at room temperature when a metal catalyst is added.

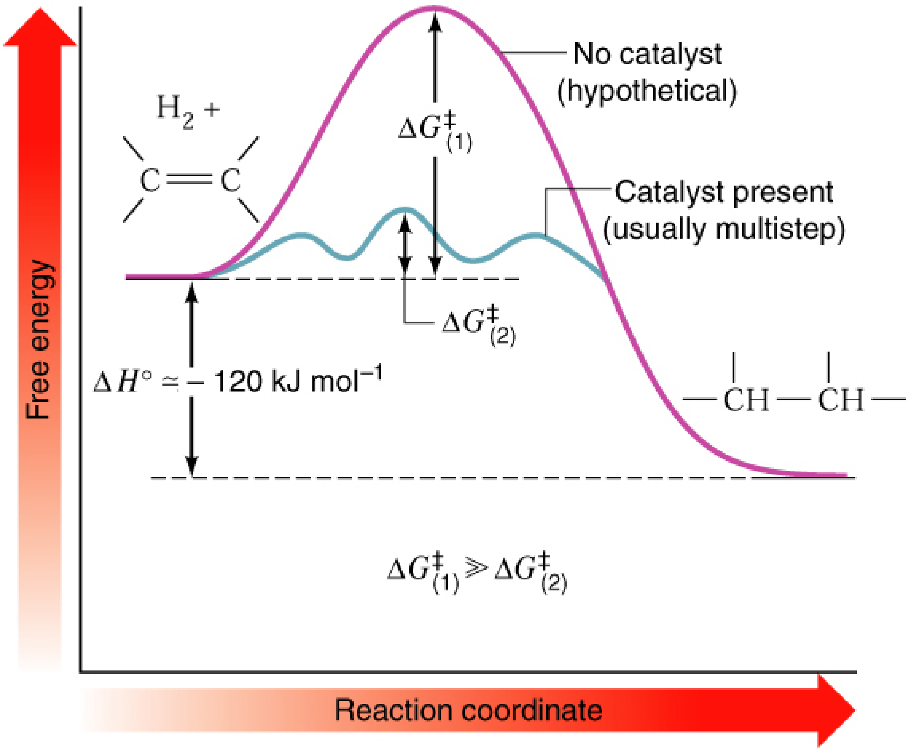


Figure 7.8 Free-energy diagram for the hydrogenation of an alkene in the presenceof a catalyst and the hypothetical reaction in the absence of a catalyst. The free energy of activation [$\Delta G^{‡}_{(1)}$] is very much larger than the largest free energy of activation for the catalyzed reaction [$\Delta G^{‡}_{(2)}$].

2. The most commonly used catalysts for hydrogenation (finely divided platinum, nickel, palladium, rhodium, and ruthenium) apparently serve to adsorb hydrogen molecules on their surface.

1) Unpaired electrons on the surface of the metal ***pair*** with the electrons of

hydrogen and bind the hydrogen to the surface.

2) The collision of an alkene with the surface bearing adsorbed hydrogen causes adsorption of the alkene.

3) A stepwise transfer of hydrogen atoms take place, and this produces an alkane before the organic molecule leaves the catalyst surface.

4) Both hydrogen atoms usually add form the same side of the molecule (***syn*** addition).

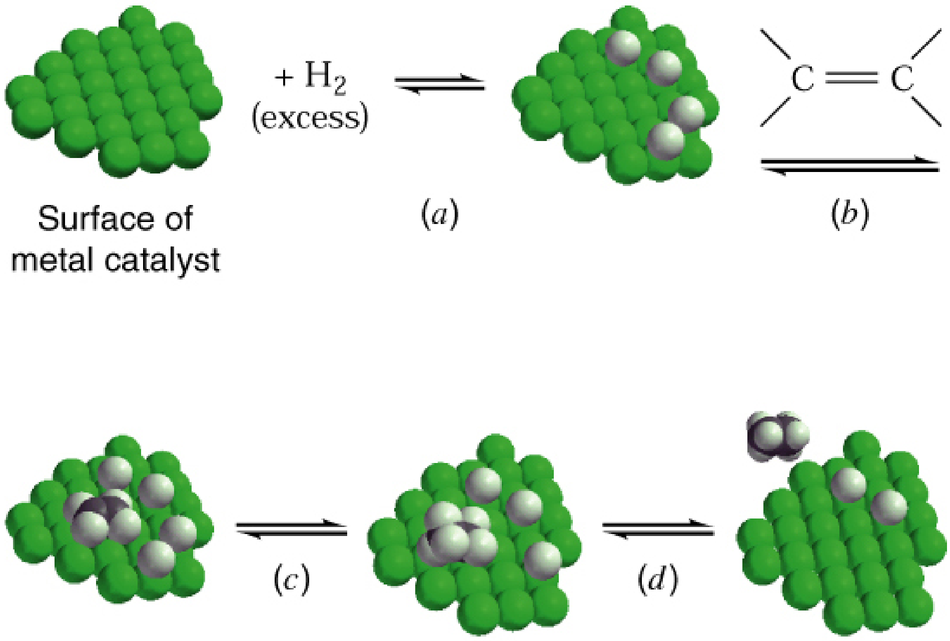
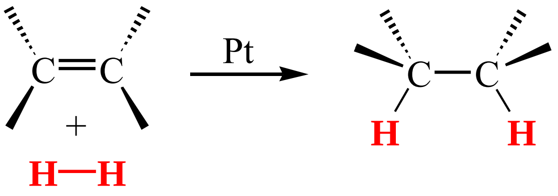


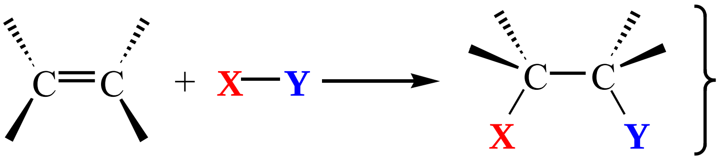
Figure 7.9 **The mechanism for the hydrogenation of an alkene as catalyzed by finely divided platinum metal: (a) hydrogen adsorption; (b) adsorption of the alkene; (c) and (d), stepwise transfer of both hydrogen atoms to the same face of the alkene (*syn* addition).**



Catalytic hydrogenation is a syn addition.

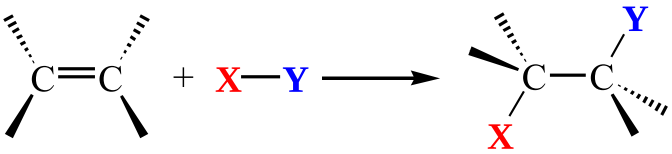
7.14A Syn and Anti Additions

1. ***Syn* addition:**



A syn addition

2. ***Anti* addition:**



A anti addition

7.15 Hydrogenation of Alkynes

1. Depending on the conditions and the catalyst employed, one or two molar equivalents of hydrogen will add to a carbon–carbon triple bond.

   1) A platinum catalyst catalyzes the reaction of an alkyne with two molar equivalents of hydrogen to give an alkane.

$$CH_3C{\equiv}CCH_3 \xrightarrow[H_2]{Pt} [CH_3CH{=}CHCH_3] \xrightarrow[H_2]{Pt} CH_3CH_2CH_2CH_3$$

7.15A Syn Addition of Hydrogen: Synthesis of *Cis*-Alkenes

1. A catalyst that permits hydrogenation of an alkyne to an alkene is the nickel boride compound called P-2 catalyst.

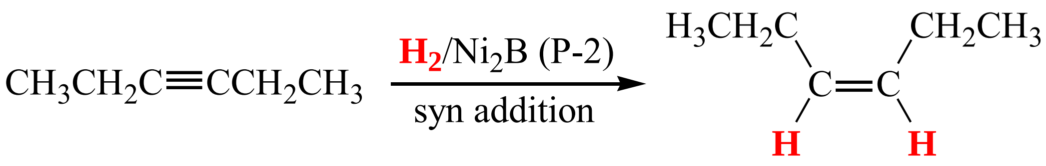
$$Ni\left(OCCH_3\right)_2 \xrightarrow[C_2H_5OH]{NaBH_4} \underset{\textbf{P-2}}{Ni_2B}$$

(the C of OCCH₃ bears a C=O)

   1) Hydrogenation of alkynes in the presence of P-2 catalyst causes **syn addition of hydrogen** to take place, and the alkene that is formed from an alkyne with an internal triple bond has the (*Z*) or cis configuration.

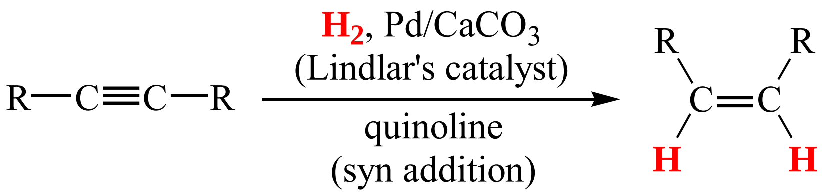
   2) The reaction take place on the surface of the catalyst accounting for the **syn**

addition.



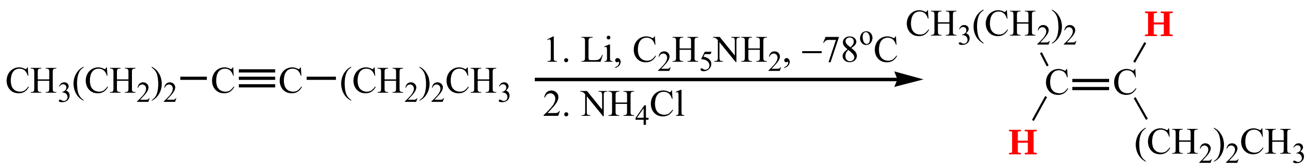
3-Hexyne **(*Z*)-3-Hexene (*cis*-3-hexene) (97%)**

2. **Lindlar's catalyst**: metallic palladium deposited on calcium carbonate and is poisoned with lead acetate and quinoline.



7.15B ANTI ADDITION OF HYDROGEN: SYNTHESIS OF *TRANS*-ALKENES

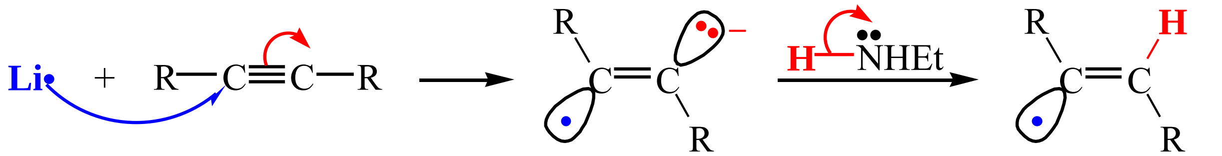
1. An **anti addition** of hydrogen atoms to the triple bond occurs when alkynes are reduced with lithium or sodium metal in ammonia or ethylamine at low temperatures.
   1) This reaction, called a **dissolving metal reduction**, produces an (*E*)- or *trans*-alkene.



4-Octyne **(*E*)-4-Octyne (*trans*-4-Octyne) (52%)**

A Mechanism for the Reduction Reaction

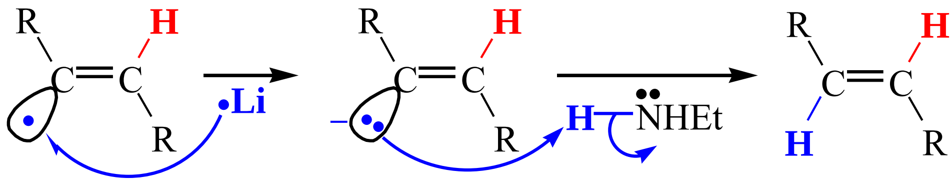
The Dissolving Metal Reduction of an Alkyne



Radical anion **Vinylic radical**

A lithium atom donates an electron to the π bond of the alkyne. An electron pair shifts to one carbon as the hybridization states change to sp^2.

The radical anion acts as a base and removes a proton from a molecule of the ethylamine.



Vinylic radical ***trans*-Vinylic anion** ***trans*-Alkene**

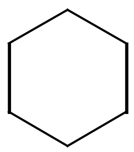
A second lithium atom donates an electron to the vinylic radical.

The anion acts as a base and removes a proton from a second molecule of ethylamine.

7.16 MOLECULAR FORMULAS OF HYDROCARBONS: THE INDEX OF HYDROGEN DEFICIENCY

1. 1-Hexene and cyclohexane have the same molecular formula (C_6H_{12}):

$CH_2{=}CHCH_2CH_2CH_2CH_3$



1-Hexene **Cyclohexane**

   1) Cyclohexane and 1-hexene are constitutional isomers.

2. Alkynes and alkenes with two double bonds (alkadienes) have the general formula C_nH_{2n-2}.

   1) Hydrocarbons with one triple bond and one double bond (alkenynes) and alkenes

with three double bonds have the general formula C_nH_{2n-4}.

$CH_2{=}CH{-}CH{=}CH_2$	$CH_2{=}CH{-}CH{=}CH{-}CH{=}CH_2$
1,3-Butadiene (C_4H_6)	**1,3,5-Hexatriene** (C_6H_8)

3. **Index of Hydrogen Deficiency** (**degree of unsaturation**, **the number of double-bond equivalence**):

   1) It is an important information about its structure for an unknown compound.
   2) The index of hydrogen deficiency is defined as the number of ***pair*** of hydrogen atoms that must be subtracted from the molecular formula of the corresponding alkane to give the molecular formula of the compound under consideration.
   3) The index of hydrogen deficiency of 1-hexene and cyclohexane:

C_6H_{14} = formula of corresponding alkane (hexane)

C_6H_{12} = formula of compound (1-hexene and cyclohexane)

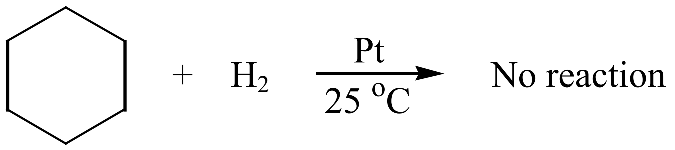
H_2 = difference = 1 pair of hydrogen atoms

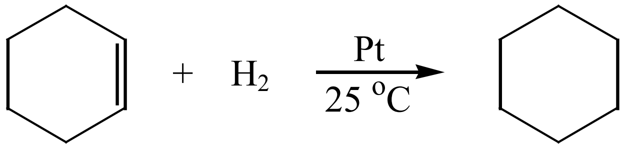
Index of hydrogen deficiency = 1

4. **Determination of the number of rings:**

   1) Each double bond consumes one molar equivalent of hydrogen; each triple bond consumes two.
   2) Rings are not affected by hydrogenation at room temperature.

$$CH_2{=}CH(CH_2)_3CH_3 \quad + \quad H_2 \xrightarrow[25\ ^{o}C]{Pt} CH_3(CH_2)_4CH_3$$





Cyclohexene

$$CH_2{=}CHCH{=}CHCH_2CH_3 \quad + \quad 2\ H_2 \xrightarrow[25\ ^{o}C]{Pt} CH_3(CH_2)_4CH_3$$

1,3-Hexadiene

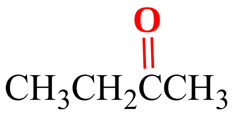
4. **Calculating the index of Hydrogen Deficiency (IHD):**

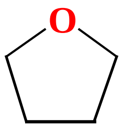
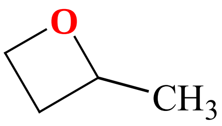
1) For compounds containing halogen atoms: **simply count the halogen atoms as hydrogen atoms**.

$$C_4H_6Cl_2 = C_4H_8 \quad \Rightarrow \quad \text{IHD} = 1$$

2) For compounds containing oxygen atoms: **ignore the oxygen atoms and calculate the IHD from the remainder of the formula**.

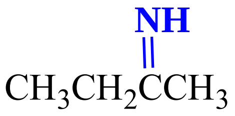
$$C_4H_8O = C_4H_8 \quad \Rightarrow \quad \text{IHD} = 1$$

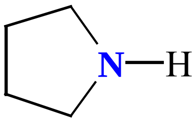
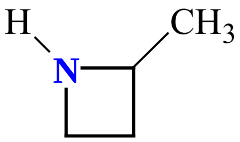
$CH_2{=}CHCH_2CH_2$**OH** $CH_3CH_2{=}CHCH_2$**OH** 

  and so on

3) For compounds containing nitrogen atoms: **subtract one hydrogen for each nitrogen atom, and then ignore the nitrogen atoms**.

$$C_4H_9N = C_4H_8 \quad \Rightarrow \quad \text{IHD} = 1$$

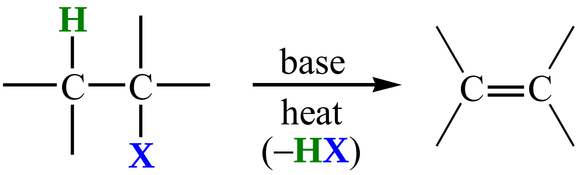
$CH_2{=}CHCH_2CH_2$**NH₂** $CH_3CH_2{=}CHCH_2$**NH₂** 

  and so on

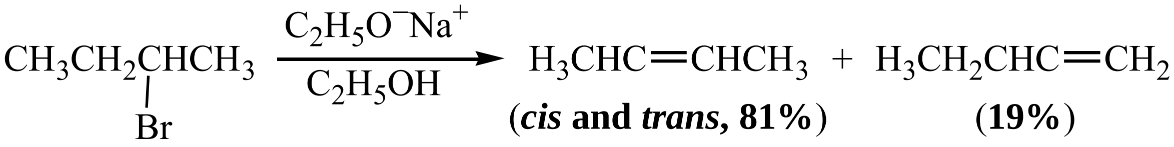
SUMMARY OF METHODS FOR THE PREPARATION OF ALKENES AND ALKYNES

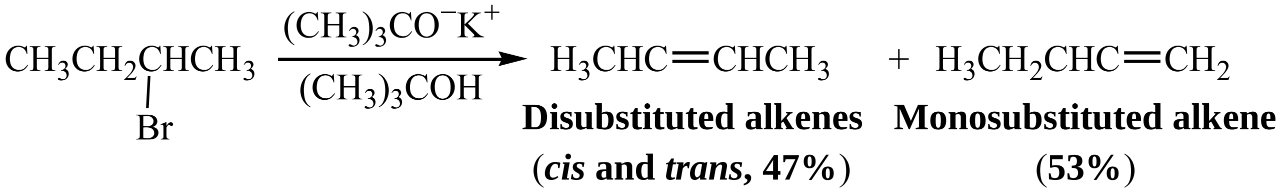
1. Dehydrohalogenation of alkyl halides (Section 7.6)

General Reaction



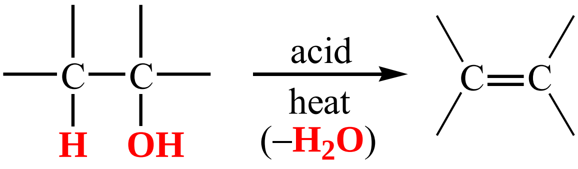
Specific Examples





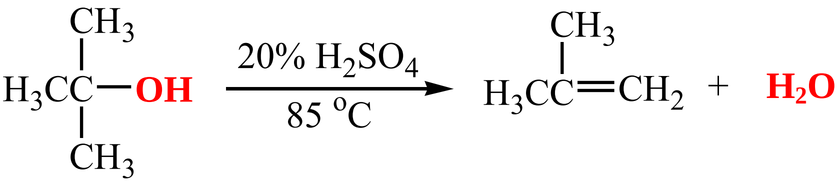
2. Dehydration of alcohols (Section 7.7 and 7.8)

General Reaction



Specific Examples

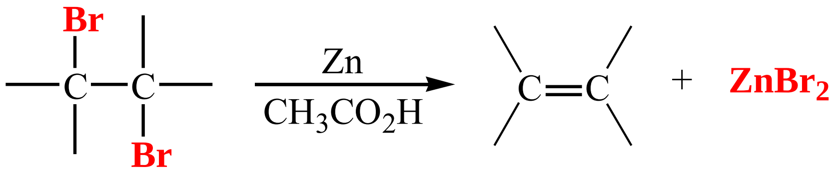
$$CH_3CH_2\mathbf{OH} \xrightarrow[180\ ^{o}C]{\text{concd } H_2SO_4} CH_2{=}CH_2 + \mathbf{H_2O}$$



SUMMARY OF METHODS FOR THE PREPARATION OF ALKENES AND ALKYNES

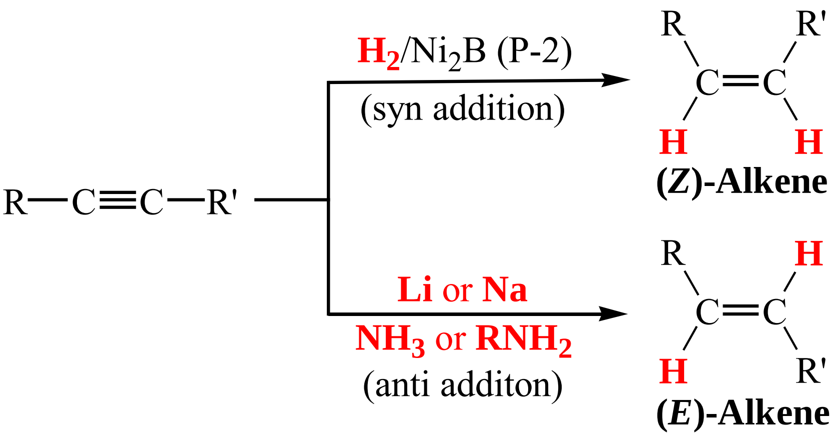
3. Debromination of *vic*-dibromides (**Section 7.9**)

General Reaction



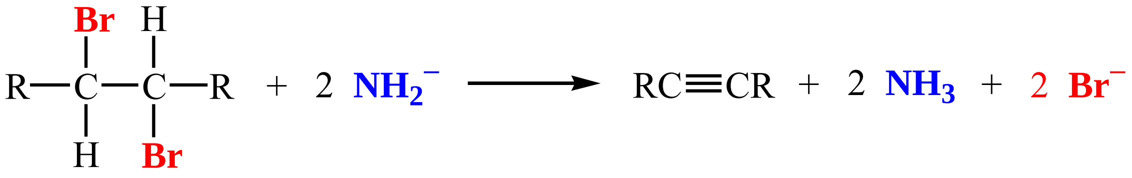
4. Hydrogenation of alkynes (**Section 7.15**)

General Reaction



5. Dehydrohalogenation of *vic*-dibromides (**Section 7.15**)

General Reaction



ALKENES AND ALKYNES II. ADDITION REACTIONS

THE SEA: A TREASURY OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS

Electron micrograph of myosin

1. The concentration of halides in the ocean is approximately 0.5 *M* in chloride, 1m*M* in bromide, and 1μ*M* in iodide.
2. Marine organisms have incorporated halogen atoms into the structures of many of their metabolites:
3. For the marine organisms that make the metabolites, some of these molecules are part of defense mechanisms that serve to promote the species' survival by deterring predators or inhibiting the growth of competing organisms.
4. For humans, the vast resource of marine natural products shows great potential as a source of new therapeutic agents.
   1) **Halomon**: in preclinical evaluation as a cytotoxic agent against certain tumor cell types.

2) **Tetrachloromertensene**:

3) **(3*R*)- and (3*S*)-Cyclocymopol monomethyl ether**: show agonistic or antagonistic effects on the human progesterone receptor, depending on which enantiomer is used

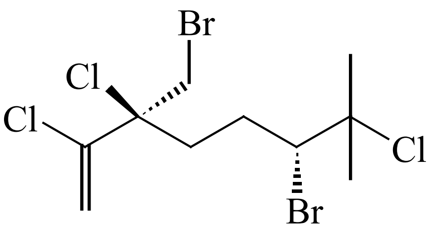
4) **Dactylyne**: an inhibitor of pentobarbital metabolism

5) **(3*E*)-Laureatin**:

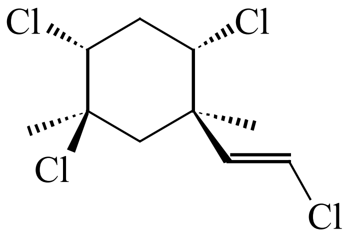
6) **Kumepaloxane**: a fish antifeedant synthesized by the Guam bubble snail *Haminoea cymbalum*, presumably as a defense mechanism for the snail.

7) **Brevetoxin B**: associated with deadly “red tides”.

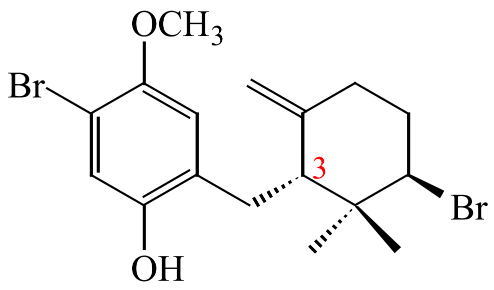
8) **Eleutherobin**: a promising anticancer agent.



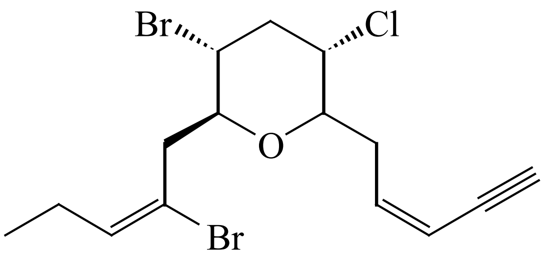
Halomon



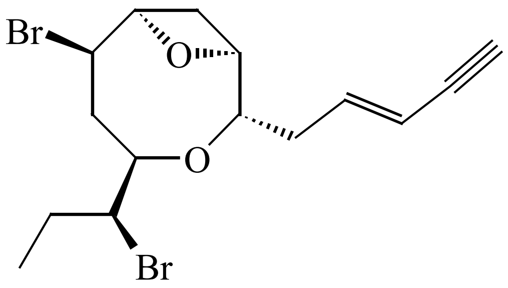
Tetrachloromertensene



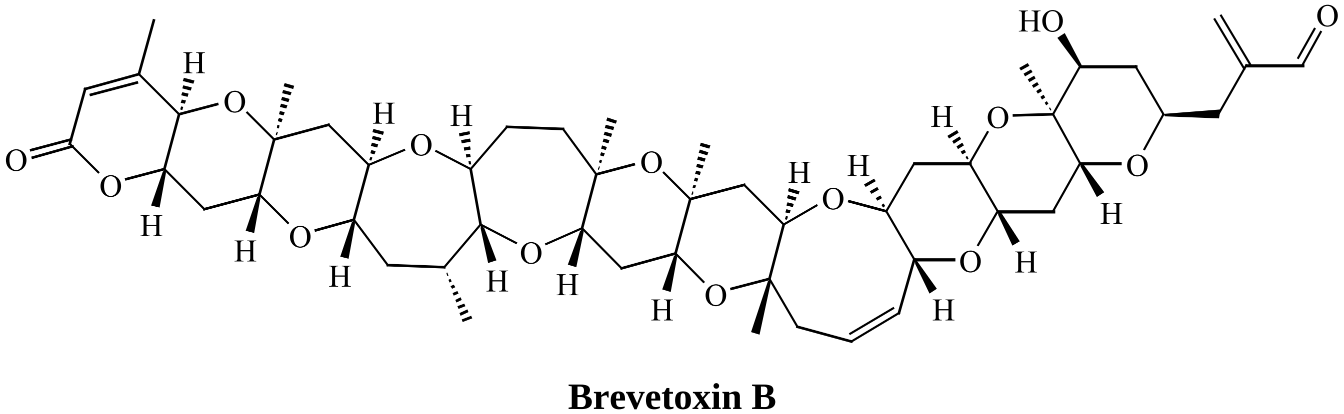
Cyclocymopol monomethyl ether



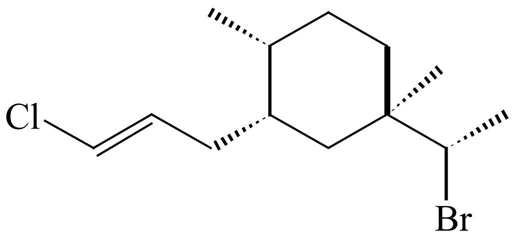
Dactylyne



(3*E*)-Laureatin



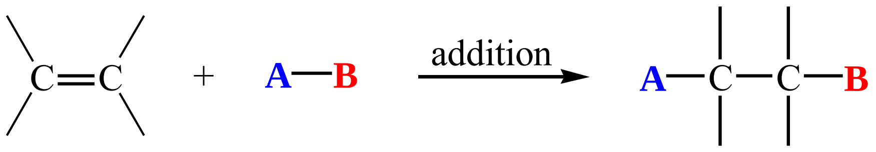
Brevetoxin B

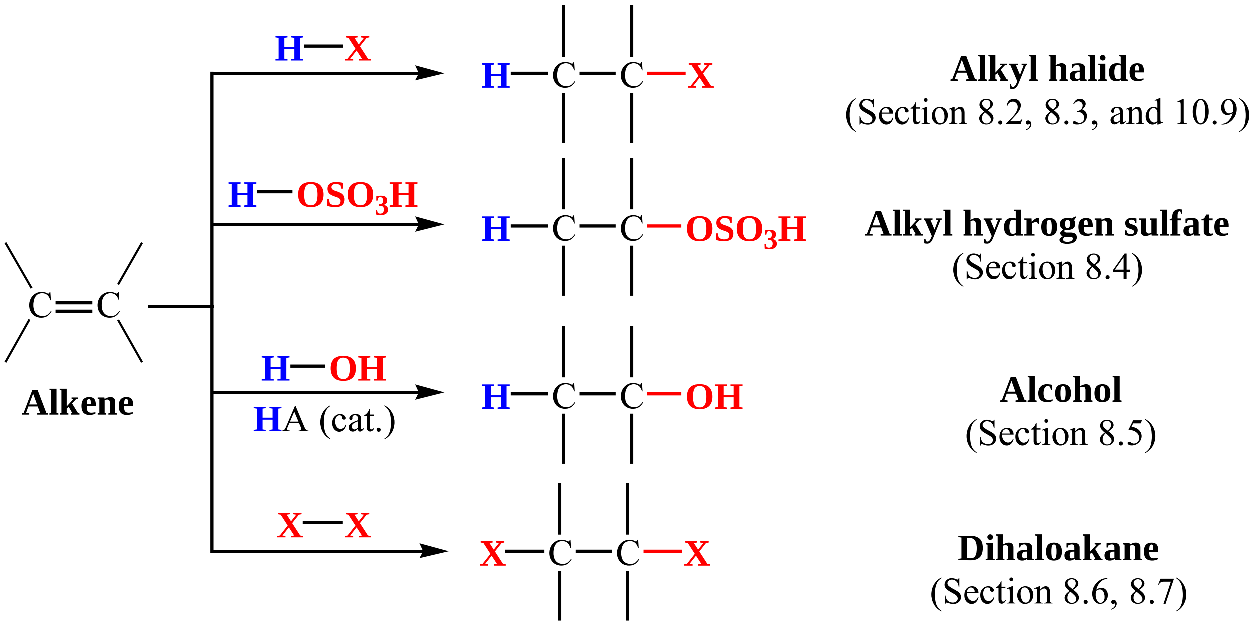


Kumepaloxane

5. The biosynthesis of halogenated marine natural products:
   1) Some of their halogens appear to have been introduced as ***electrophiles*** rather than as Lewis bases or nucleophiles, which is their character when they are solutes in seawater.
   2) Many marine organisms have enzymes called haloperoxidases that convert nucleophilic iodide, bromide, or chloride anions into electrophilic species that react like I^+, Br^+ or Cl^+.
   3) In the biosynthetic schemes proposed for some halogenated natural products, positive halogen intermediates are attacked by electrons from the π bond of an alkene or alkyne in an addition reaction.

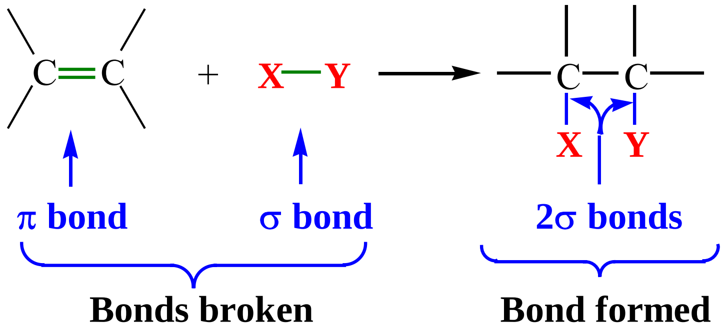
8.1 INTRODUCTION: ADDITIONS TO ALKENES



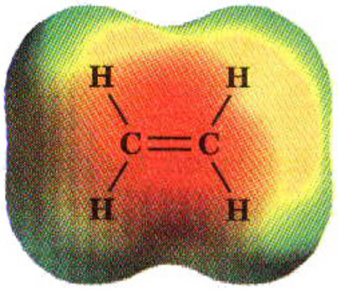


8.1A CHARACTERISTICS OF THE DOUBLE BOND:

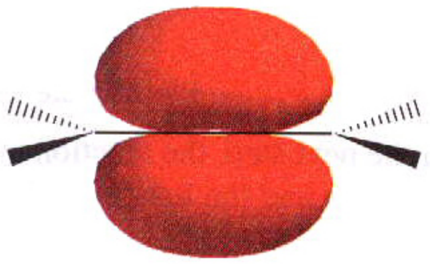
1. An addition results in the conversion of one π bond and one σ bond into two σ bonds:
   1) π bonds are weaker than that of σ binds ⇒ energetically favorable.



2. The electrons of the π bond are exposed ⇒ the π bond is particularly susceptible to **electrophiles** (electron-seeking reagents).



An electrostatic potential map for ethane shows the higher density of negative charge in the region of the π bond.

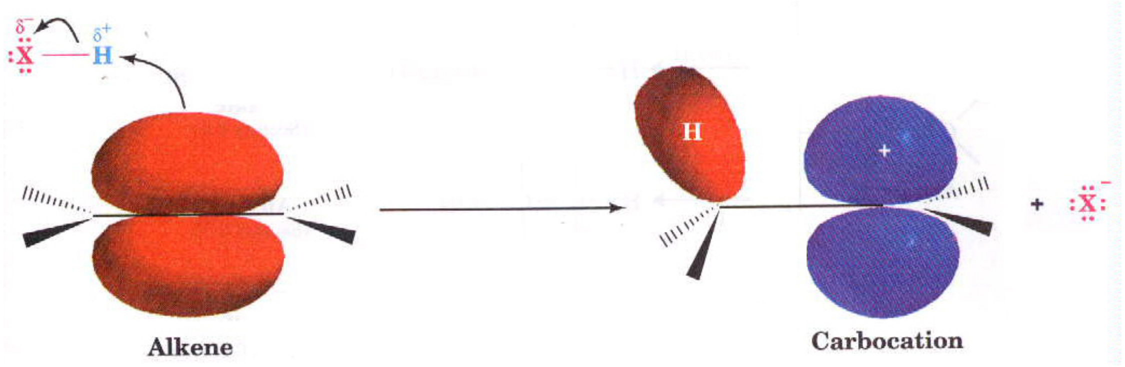


The electron pair of the π bond is distributed throughout both lobes of the π molecular orbital.

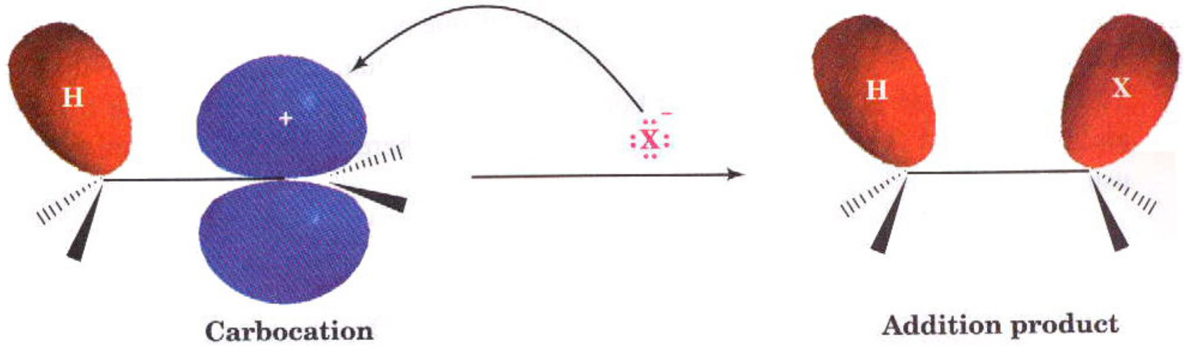
   1) **Electrophilic:** electron-seeking.
   2) Electrophiles include:
      i) **Positive reagents**: protons (H^+).
      ii) **Neutral reagents**: bromine (because it can be polarized so that one end is positive).
      iii) **Lewis acids**: BF_3 and $AlCl_3$.
      iv) **Metal ions** that contain vacant orbitals: the silver ion (Ag^+), the mercuric ion (Hg^{2+}), and the platinum ion (Pt^{2+}).

8.1B THE MECHANISM OF THE ADDITION OF HX TO A DOUBLE BOND:

1. The H^+ of HX reacts with the alkene by using the two electons of the π bond to form a σ bond to one of the carbon atoms ⇒ leaves a vacant *p* orbital and a + charge on the other carbon ⇒ formation of a carbocation and a halide ion:

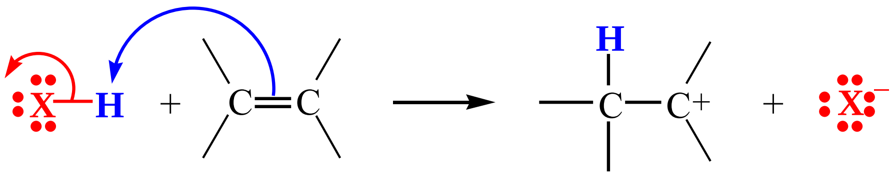


2. The carbocation is highly reactive and combines with the halide ion:



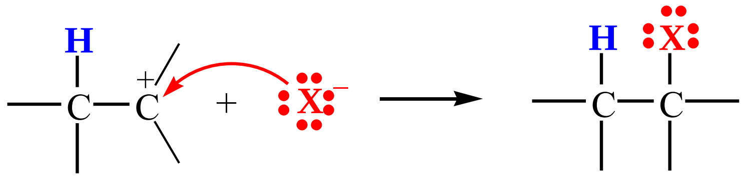
8.1C ELECTROPHILES ARE LEWIS ACIDS:

1. **Electrophiles**: molecules or ions that can accept an electron pair ⇒ Lewis acids.
2. **Nucleophiles**: molecules or ions that can furnish an electron pair ⇒ Lewis bases.
3. Any reaction of an electrophile also involves a nucleophile.
4. In the protonation of an alkene:
   1) The **electrophile** is the proton donated by an acid.
   2) The **nucleophile** is the alkene.



Electrophile   Nucleophile

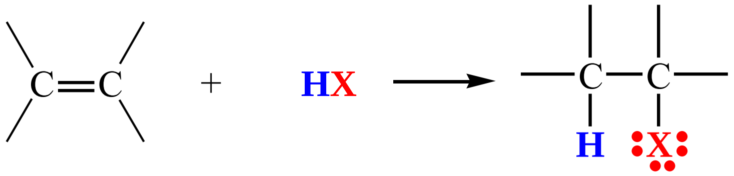
5. The carbocation reacts with the halide in the next step:



Electrophile   Nucleophile

8.2 ADDITION OF HYDROGEN HALIDES TO ALKENE: MARKOVNIKOV'S RULE

1. Hydrogen halides (HI, HBr, HCl, and HF) add to the double bond of alkenes:

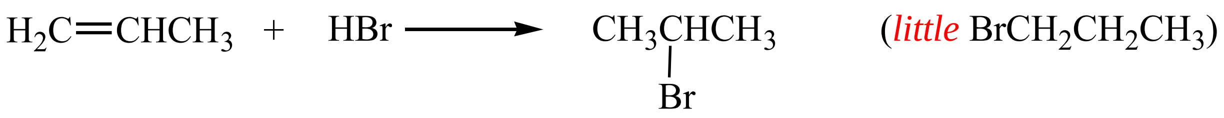


2. The addition reactions can be carried out:
   1) By dissolving the HX in a solvent such as acetic acid or CH_2Cl_2.
   2) By bubbling the gaseous HX directly into the alkene and using the alkene itself as the solvent.
      i) HF is prepared as polyhydrogen fluoride in pyridine.

3. The order of reactivity of the HX is HI > HBr > HCl > HF:
   i) Unless the alkene is highly substituted, HCl reacts so slowly that the reaction is not an useful preparative method.
   ii) HBr adds readily, but, unless precautions are taken, the reaction may follow an alternate course.

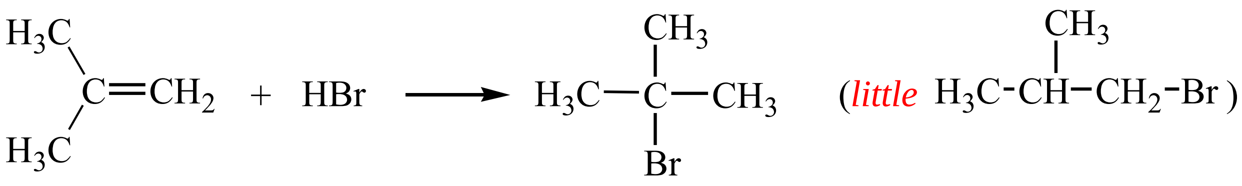
4. Adding silica gel or alumina to the mixture of the alkene and HCl or HBr in CH_2Cl_2 increases the rate of addition dramatically and makes the reaction an easy one to carry out.

5. The ***regioselectivity*** of the addition of HX to an unsymmetrical alkenes:
   i) The addition of HBr to propene: the main product is 2-bromopropane.



2-Bromopropane **1-Bromopropane**

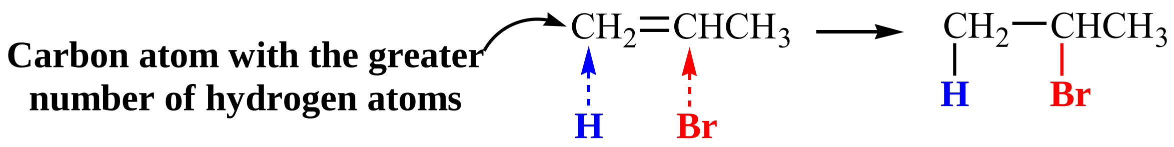
   ii) The addition of HBr to 2-methylpropene: the main product is *tert*-butyl bromide.



2-Methylpropene (isobutylene) ***tert*-Butyl bromide** **Isobutyl bromide**

8.2A MARKOVNIKOV'S RULE:

1. Russian chemist Vladimir Markovnikov in 1870 proposed the following rule:
   1) "**If an unsymmetrical alkene combines with a hydrogen halide, the halide ion adds to the carbon atom with fewer hydrogen atoms**" (**The addition of HX to an alkene, the hydrogen atom adds to the carbon atom of the double that already has the greater number of hydrogen atoms**).

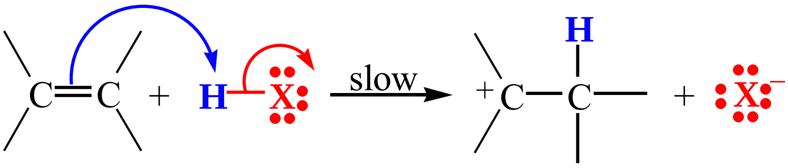


   i) **Markovnikov addition:**
   ii) **Markovnikov product:**

A Mechanism for the Reaction

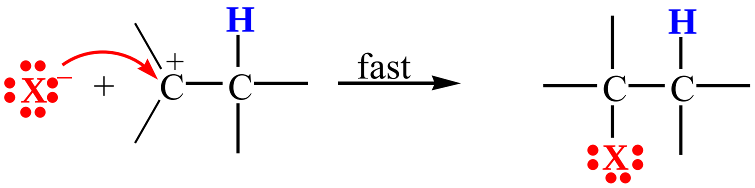
Addition of a Hydrogen Halide an Alkene

Step 1



The π electron of the alkene form a bond with a proton from HX to form a carbocation and a halide ion.

Step 2



The halide ion reacts with the carbocation by donating an electron pair; the result is an alkyl halide.

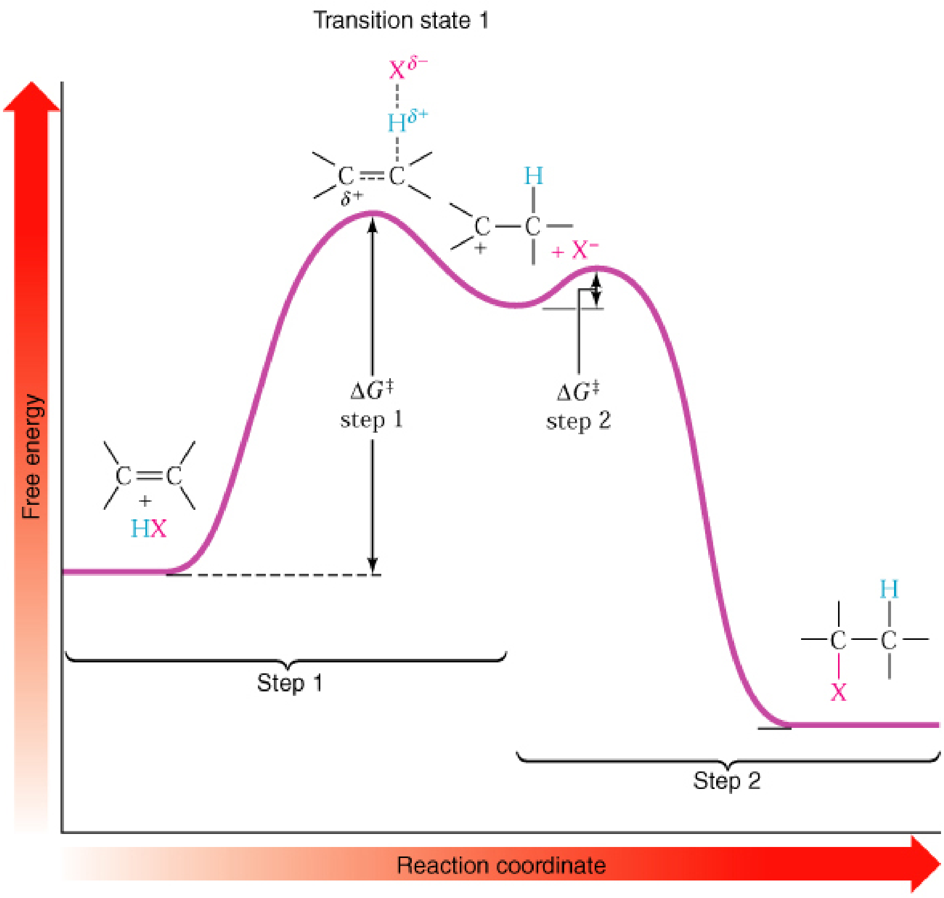


Figure 8.1 **Free-energy diagram for the addition of HX to an alkene. The free energy of activation for step 1 is much larger than that for step 2.**

2. **Rate-determining step**:

1) Alkene accepts a proton from the HX and forms a carbocation in **step 1**.

2) This step is highly endothermic and has a high free energy of activation ⇒ it takes place slowly.

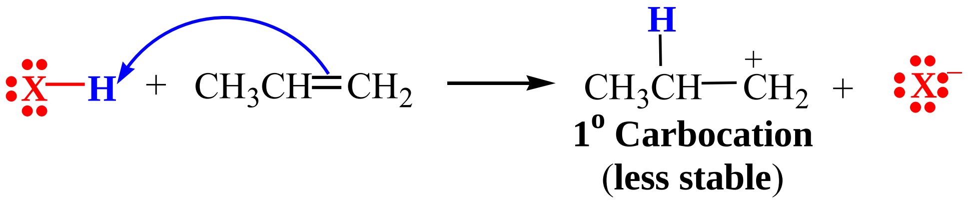
3. **Step 2**:

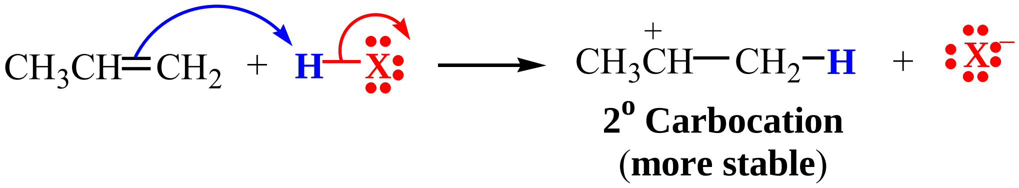
1) The highly reactive carbocation stabilizes itself by combining with a halide ion.

2) This exothermic step has a very low free energy of activation ⇒ it takes place rapidly.

8.2B THEORETICAL EXPLANATION OF MARKOVNIKOV'S RULE:

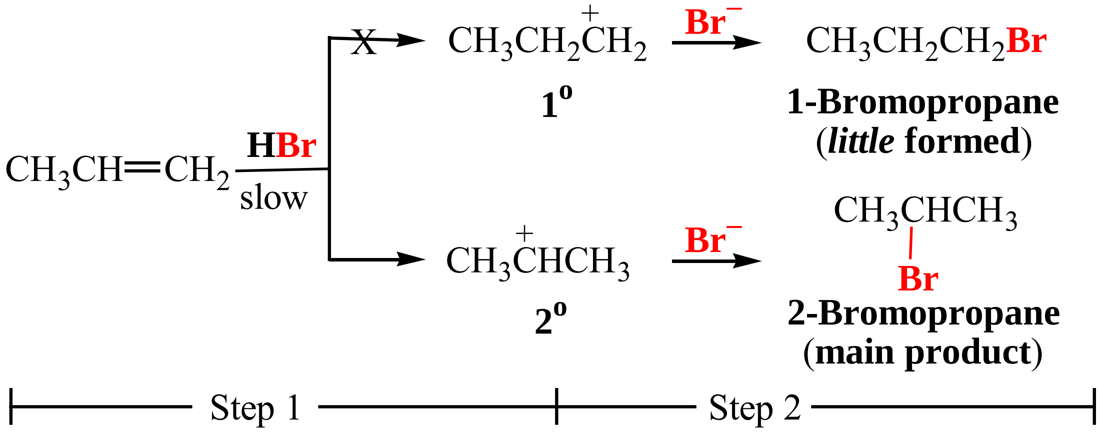
1. The step 1 of the addition reaction of HX to an unsymmetrical alkene could conceivably lead to two different carbocations:





2. These two carbocations are not of equal stability.

1) The 2° carbocation is ***more stable*** ⇒ accounts for the correct predication of the overall addition by Markovnikov's rule.



2) The more stable 2° carbocation is formed preferentially in the first step ⇒ the chief product is 2-bromopropane.

3. The more stable carbocation predominates because it is formed faster.

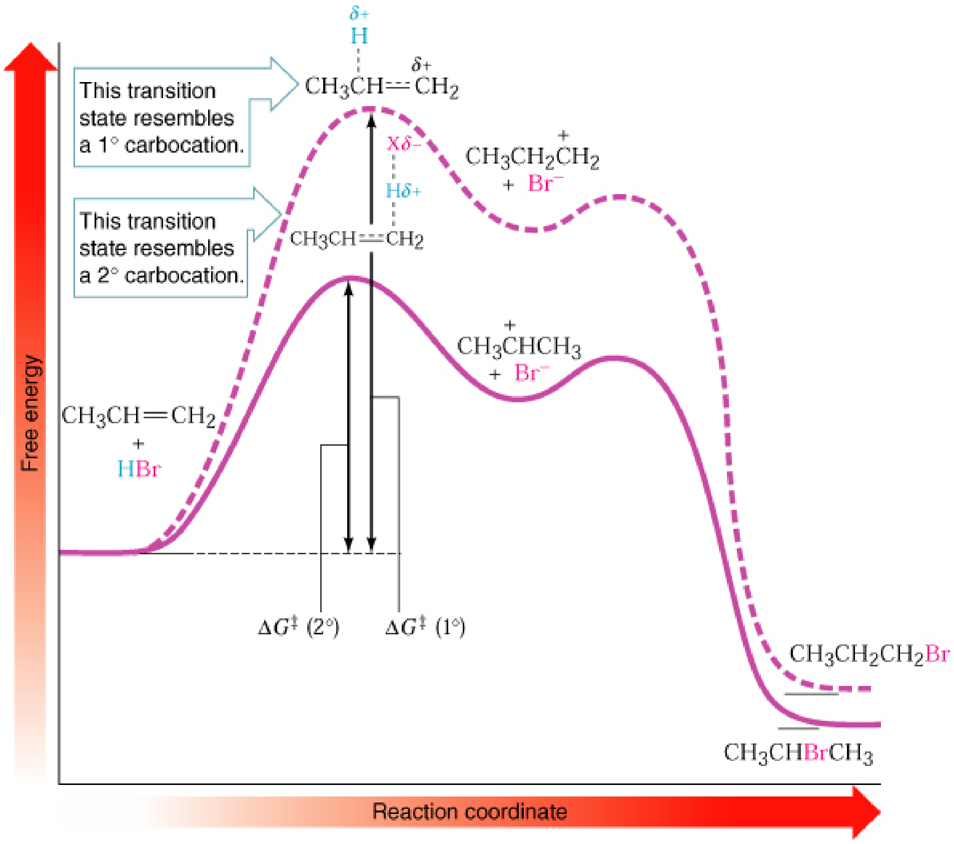


Figure 8.2 **Free-energy diagrams for the addition of HBr to propene. $\Delta G^{\ddagger}(2°)$ is less than $\Delta G^{\ddagger}(1°)$.**

1) The transition state resembles the more stable 2° carbocation ⇒ the reaction leading to the 2° carbocation (and ultimately to 2-bromopropane) has the lower free energy of activation.

2) The transition state resembles the less stable 1° carbocation ⇒ the reaction leading to the 1° carbocation (and ultimately to 1-bromopropane) has a higher free energy of activation.

3) The second reaction is much slower and does not compete with the first one.

4. The reaction of HBr with 2-methylpropene produces only *tert*-butyl bromide.

1) The difference between a 3° and a 1° carbocation.

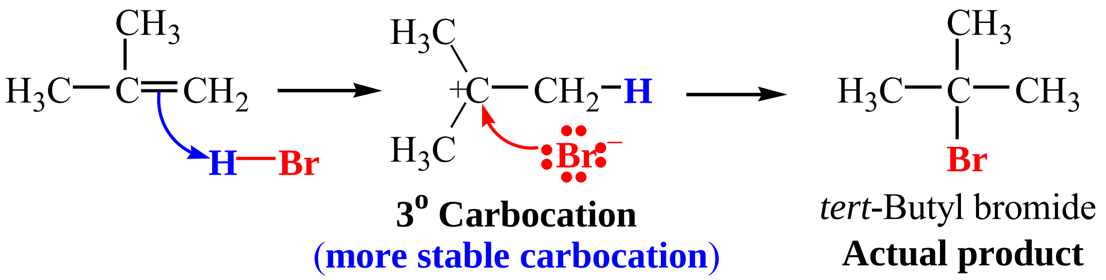
2) The formation of a 1° carbocation is ***required*** ⇒ isobutyl bromide is ***not*** obtained as a product of the reaction.

3) The reaction would have a much higher free energy of activation than that leading to a 3° carbocation.

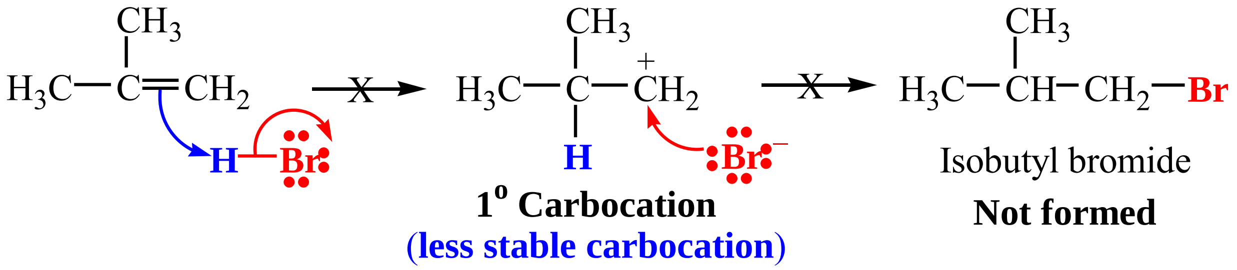
A Mechanism for the Reaction

Addition of HBr to 2-Methylpropene

This reaction takes place:



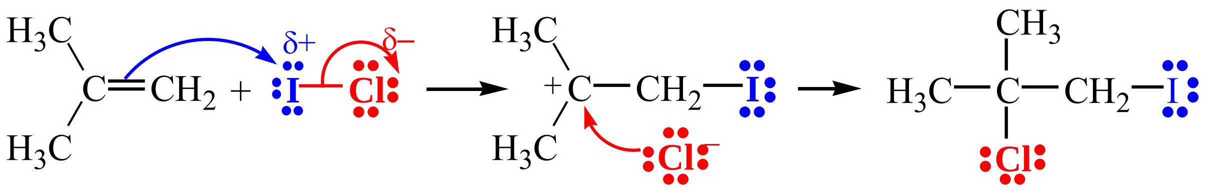
This reaction ***does not*** occur appreciably:



5. When the carbocation initially formed in the addition of HX to an alkene can rearrange to a more stable one ⇒ rearrangements invariably occur.

8.2C Modern Statement of Markovnikov's Rule:

1. ***In the ionic addition of an unsymmetrical reagent to a double bond, the positive portion of the adding reagent attaches itself to a carbon atom of the double bond so as to yield the more stable carbocation as an intermediate*.**
   1) This is the step that occurs first (before the addition of the negative portion of the adding reagent) ⇒ it is the step that determines the overall orientation of the reaction.



2-methylpropene **2-Chloro-1-iodo-2-methylpropane**

8.2D Regioselective Reactions:

1. ***When a reaction that can potentially yield two or more constitutional isomers actually produces only one (or a predominance of one), the reaction is said to be regioselective*.**

8.2E An Exception to Markovnikov's Rule:

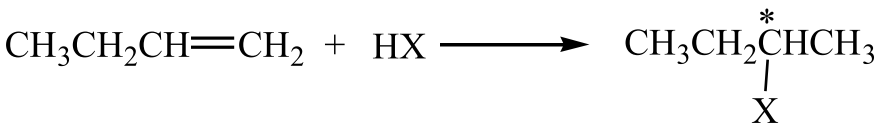
1. When alkenes are treated with HBr in the presence of ***peroxides*** (i.e., compounds with the general formula ROOR) the addition occurs in an anti-Markovnikov manner in the sense that the hydrogen atom becomes attached to the carbon atom with fewer hydrogen atoms.

$$CH_3CH{=}CH_2 + HBr \xrightarrow{ROOR} CH_3CH_2CH_2Br$$

   1) This anti-Markovnikov addition occurs ***only when HBr is used in the presence of peroxides*** and does not occur significantly with HF, HCl, and HI even when peroxides are present.

8.3 STEREOCHEMISTRY OF THE IONIC ADDITION TO AN ALKENE

1. The addition of HX to 1-butene leads to the formation of 2-halobutane:

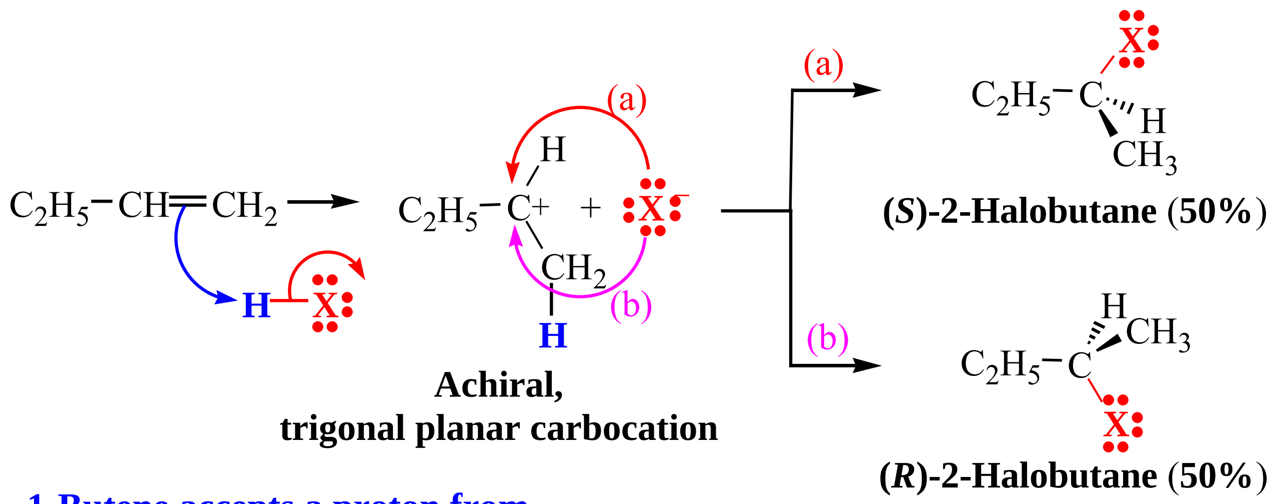


1) The product has a stereocenter and can exist as a pair of enantiomers.
2) The carbocation intermediate formed in the first step of the addition is trigonal plannar and is ***achiral***.
3) When the halide ion reacts with this achiral carbocation in the second step, ***reaction is equally likely at either face***.

   i) The reactions leading to the two enantiomers occur at the same rate, and the enantiomers are produced in equal amounts ***as a racemic form***.

The Stereochemistry of the Reaction

Ionic Addition to an Alkene

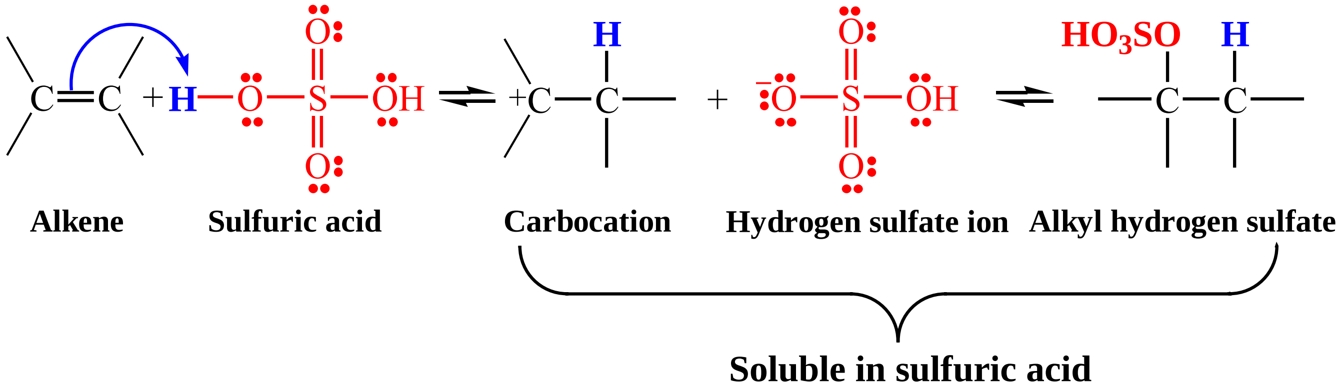


1-Butene accepts a proton from HX to form an achiral carbocation.

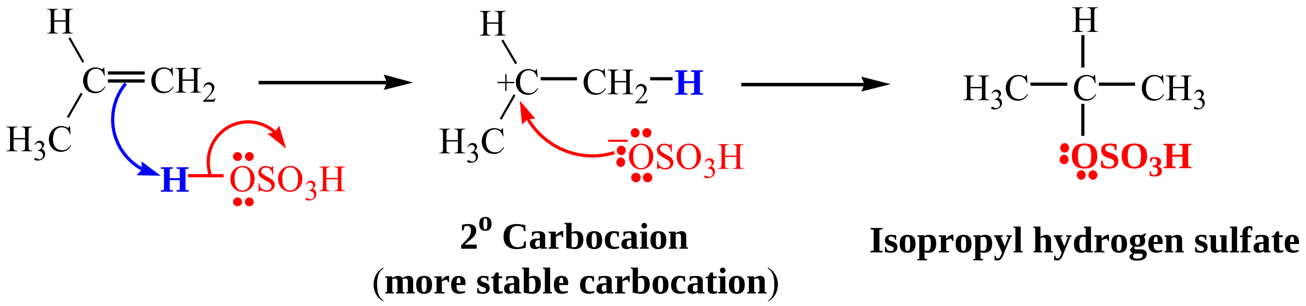
The carbocation reacts with the halide ion at equal rates by path (a) or (b) to form the enantiomers as a racemate.

8.4 ADDITION OF SULFURIC ACID TO ALKENES

1. When alkenes are treated with **cold** concentrated sulfuric acid, ***they dissolve*** because they react by addition to form **alkyl hydrogen sulfates**.
2. The mechanism is similar to that for the addition of HX:
   1) In the first step, the alkene accepts a **H^+** form sulfuric acid to form a **carbocation**.
   2) In the second step, the carbocation reacts with a hydrogen sulfate ion to form an **alkyl hydrogen sulfate**.

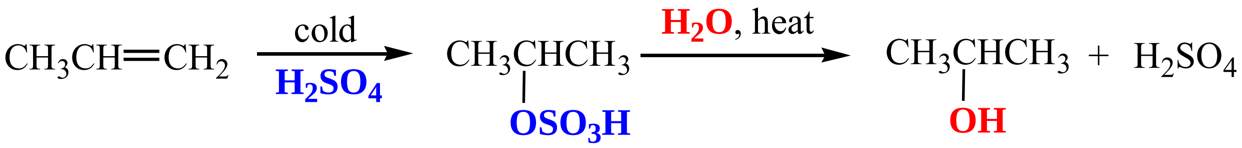


3. The addition of H_2SO_4 is regioselective and follows Markovnikov's rule:



8.4A ALCOHOLS FROM ALKYL HYDROGEN SULFATES:

1. Alkyl hydrogen sulfates can be easily hydrolyzed to alcohols by **heating** them with water.

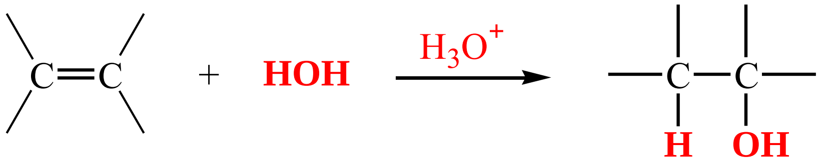


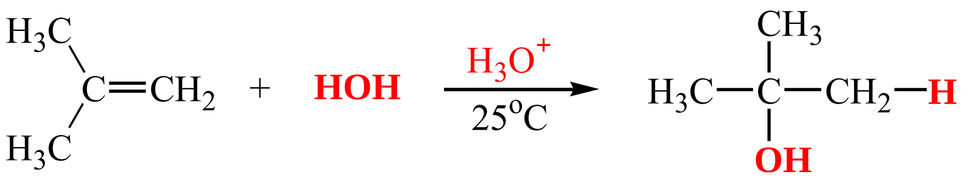
   1) The overall result of the addition of sulfuric acid to an alkene followed by

hydrolysis is the Markovnikov addition of **H–** and **–OH**.

8.5 ADDITION OF WATER TO ALKENES: ACID-CATALYZED HYDRATION

1. The acid-catalyzed addition of water to the double bond of an alkene is a method for the preparation of low molecular weight alcohols that has its greatest utility in large-scale industrial processes.
   1) The acids most commonly used to catalyze the hydration of alkenes are dilute solutions of sulfuric acid and phosphoric acid.
   2) The addition of water to a double bond is usually regioselective and follows Markovnikov's rule.





2-Methylpropene (isobutylene) **_tert_-Butyl alcohol**

2. The acid-catalyzed hydration of alkenes follows Markovnikov's rule ⇒ the reaction does not yield 1° alcohols except in the special case of the hydration of ethene.

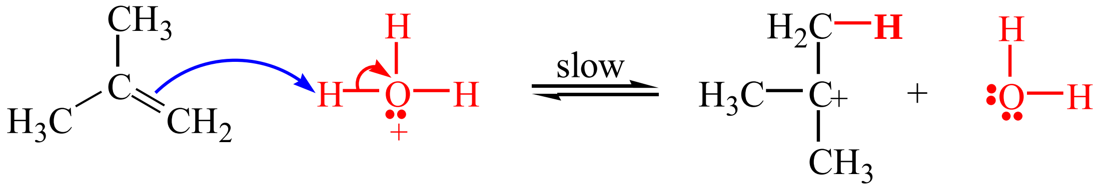
$$H_2C{=}CH_2 \; + \; \mathbf{HOH} \xrightarrow[300^{\circ}C]{H_3PO_4} CH_3CH_2OH$$

3. The mechanism for the hydration of an alkene is the reverse of the mechanism for the dehydration of an alcohol.

A Mechanism for the Reaction

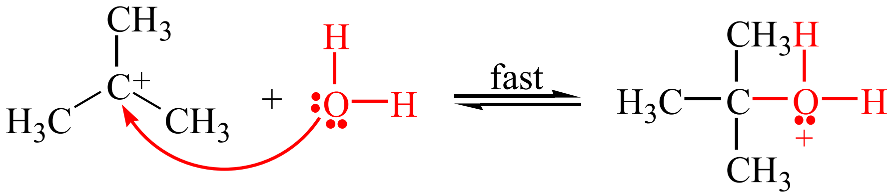
Acid-Catalyzed Hydration of an Alkene

Step 1



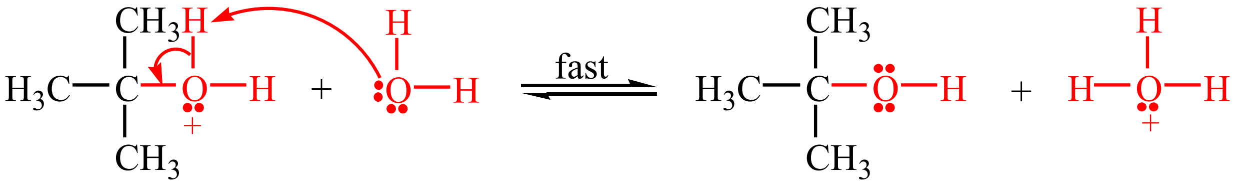
The alkene accepts a proton to form the more stable 3° carbocation.

Step 2



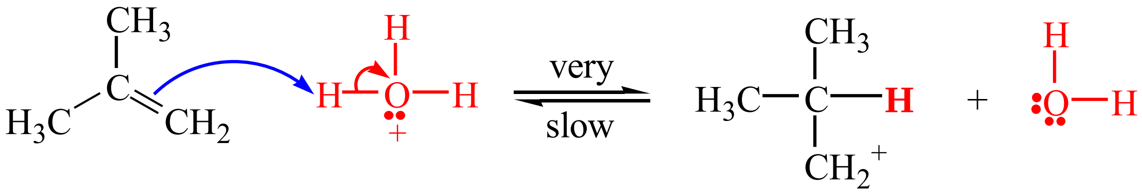
The carbocation reacts with a molucule of water to form a protonated alcohol.

Step 3



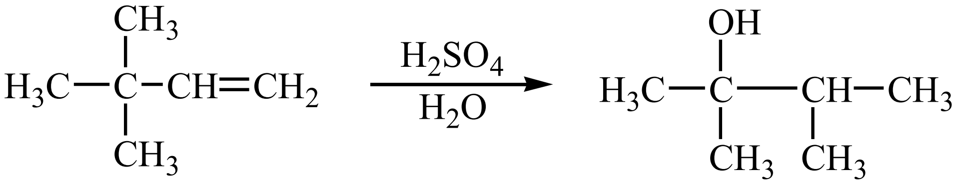
A transfer of a proton to a molecule of water leads to the product.

4. The rate-determining step in the ***hydration*** mechanism is step 1: the formation of the carbocation ⇒ accounts for the Markovnikov addition of water to the double bond.
   1) The more stable *tert*-butyl cation is formed rather than the much less stable isobutyl cation in step 1 ⇒ the reaction produces *tert*-butyl alcohol.



For all practiacl purposes this reaction does not take place because it produces a 1° carbocation.

5. The ultimate products for the ***hydration of alkenes*** or ***dehydration of alcohols*** are governed by the position of an equilibrium.
   1) The ***dehydration of an alcohol*** is best carried out using a concentrated acid so that the concentration of water is low.
      i) The water can be removed as it is formed, and it helps to use a high temperature.
   2) The ***hydration of an alkene*** is best carried out using dilute acid so that the concentration of water is high.
      i) It helps to use a lower temperature.
6. The reaction involves the formation of a carbocation in the first step ⇒ the carbocation **rearranges** to a more stable one if such a rearrangement is possible.



3,3-Dimethyl-1-butene **2,3-Dimethyl-2-butanol (major product)**

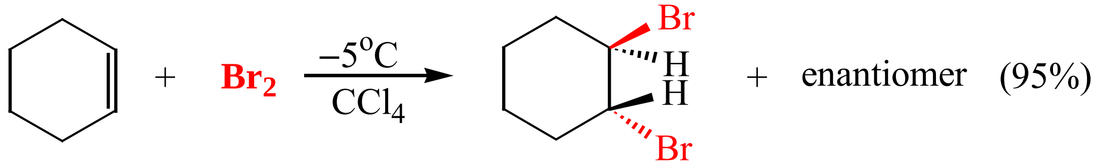
7. **Oxymercuration-demercuration** allows the Markovnikov addition of **H–** and **–OH** ***without rearrangements***.
8. **Hydroboration-oxidation** permits the *anti*-Markovnikov and ***syn addition*** of **H–** and **–OH** ***without rearrangements***.

8.6 Addition of Bromine and Chlorine to Alkenes

1. Alkenes react rapidly with chlorine and bromine in non-nucleophilic solvents to form vicinal dihalides.

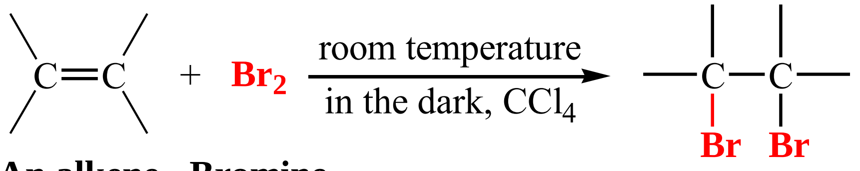
$$CH_3CH{=}CHCH_3 + Cl_2 \xrightarrow{-9^{o}C} CH_3CH(Cl){-}CH(Cl)CH_3 \quad (100\%)$$

$$CH_3CH_2CH{=}CH_2 + Cl_2 \xrightarrow{-9^{o}C} CH_3CH_2CH(Cl){-}CH_2(Cl) \quad (97\%)$$



***trans*-1,2-Dibromocyclohexane**
(as a racemic form)

2. A test for the presence of carbon-carbon multiple bonds:



An alkene **Bromine**
(colorless)(red brown)

***vic*-Dibromide**
(colorless)

Rapid decolorization of Br_2/CCl_4 is a test for alkenes and alkynes.

1) Alkanes do not react appreciably with bromine or chlorine at room temperature and in the absence of light.

$$R{-}H + Br_2 \xrightarrow[\text{in the dark, } CCl_4]{\text{room temperature}} \text{no appreciable reaction}$$

Alkane **(colorless)** **Bromine** **(red brown)**

8.6A Mechanism of Halogen Addition:

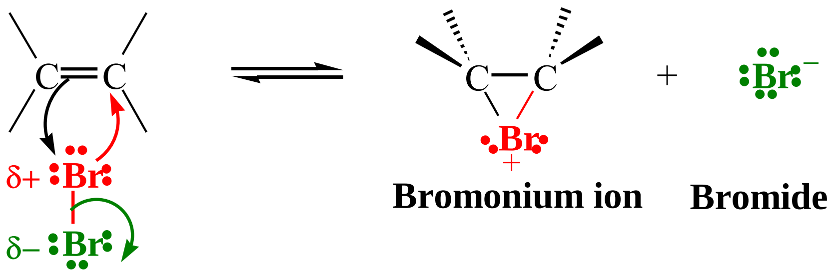
1. In the first step, the π electrons of the alkene double bond attack the halogen. (In the absence of oxygen, some reactions between alkenes and chlorine proceed

through a radical mechanism)

An Ionic Mechanism for the Reaction

Addition of Bromine to an Alkene

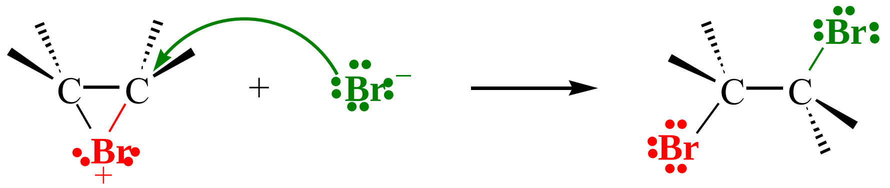
Step 1



Bromonium ion **Bromide ion**

A bromine molecule becomes polarized as it approaches the alkene. The polarized bromine molecule transfers a positive bromine atom (with six electrons in its valence shell) to the alkene resulting in the formation of a bromonium ion.

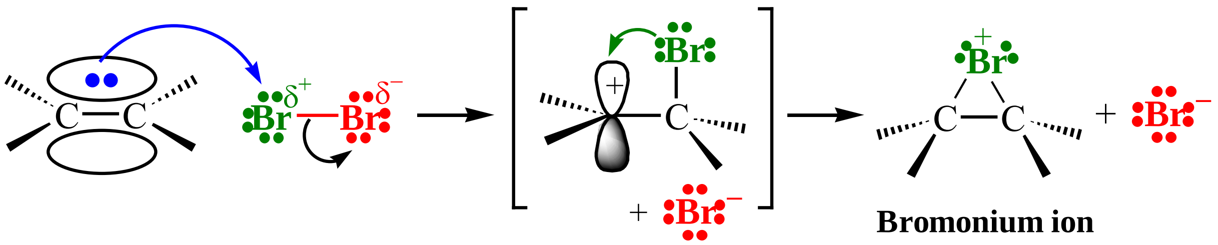
Step 2



Bromonium ion **Bromide ion** ***vic*-Dibromide**

A bromide ion attacks at the back side of one carbon (or the other) of the bromonium ion in an S_N2 reacion causing the ring to open and resulting in the formation of a *vic*-dibromide.

1) The bromine molecule becomes ***polarized*** as the π electrons of the alkene approaches the bromine molecule.
2) The electrons of the Br–Br bond drift in the direction of the bromine atom more distant from the approaching alkene ⇒ the more distant bromine develops a **partial negative charge**; the nearer bromine becomes **partially positive**.
3) Polarization weakens the Br–Br bond, causing it to ***break heterolytically*** ⇒ a bromide ion departs, and a ***bromonium ion*** forms.

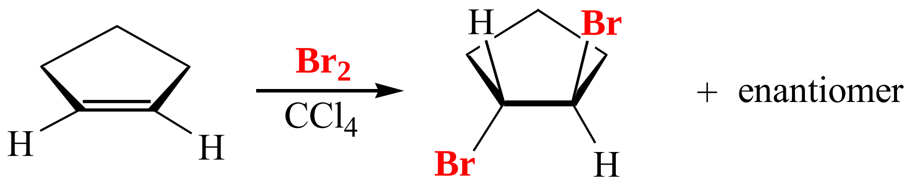


i) In the bromonium ion a positively charged bromine atom is bonded to two carbon atoms by ***twwo pairs of electrons***: one pair from the π bond of the alkene, the other pair from the bromine atom (one of its unshared pairs) ⇒ all the atoms of the bromonium ion have an octet of electrons.

2. In the second step, the bromide ion produced in step 1 attacks the back side of one of the carbon atoms of the bromonium ion.
   1) The nucleophilic attack results in the formation of a *vic*-dibromide by opening the three-membered ring.
   2) The bromide ion acts as a nucleophile while the positive bromine of the bromonium ion acts as a leaving group.

8.7 STEREOCHEMISTRY OF THE ADDITION OF HALOGENS TO ALKENES

1. **Anti addition** of bromine to cyclopentene:

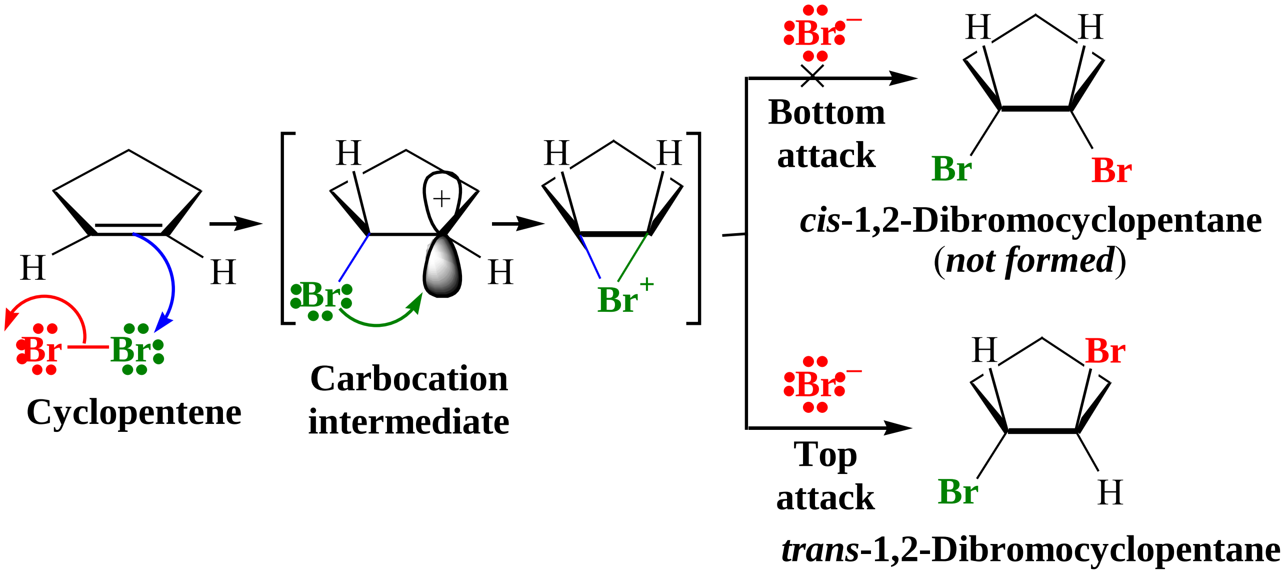


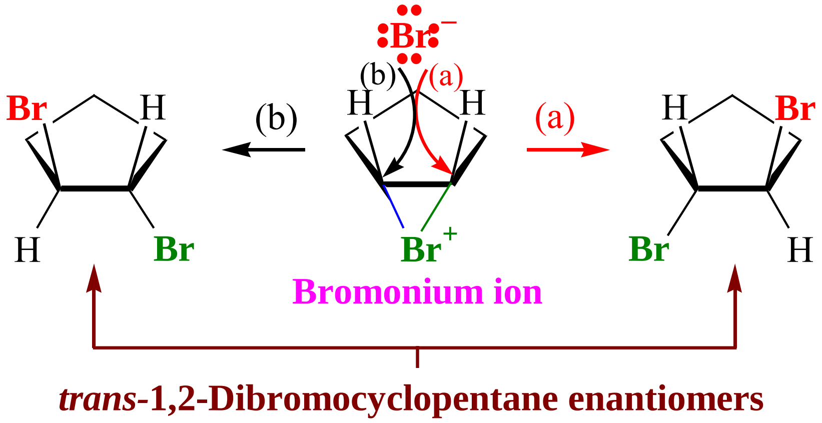
***trans*-1,2-Dibromocyclopentane**

   1) A bromonium ion formed in the first step.
   2) A bromide ion attacks a carbon atom of the ring from the opposite side of the bromonium ion.
   3) Nucleophilic attack by the bromide ion causes ***inversion of the configuration of***

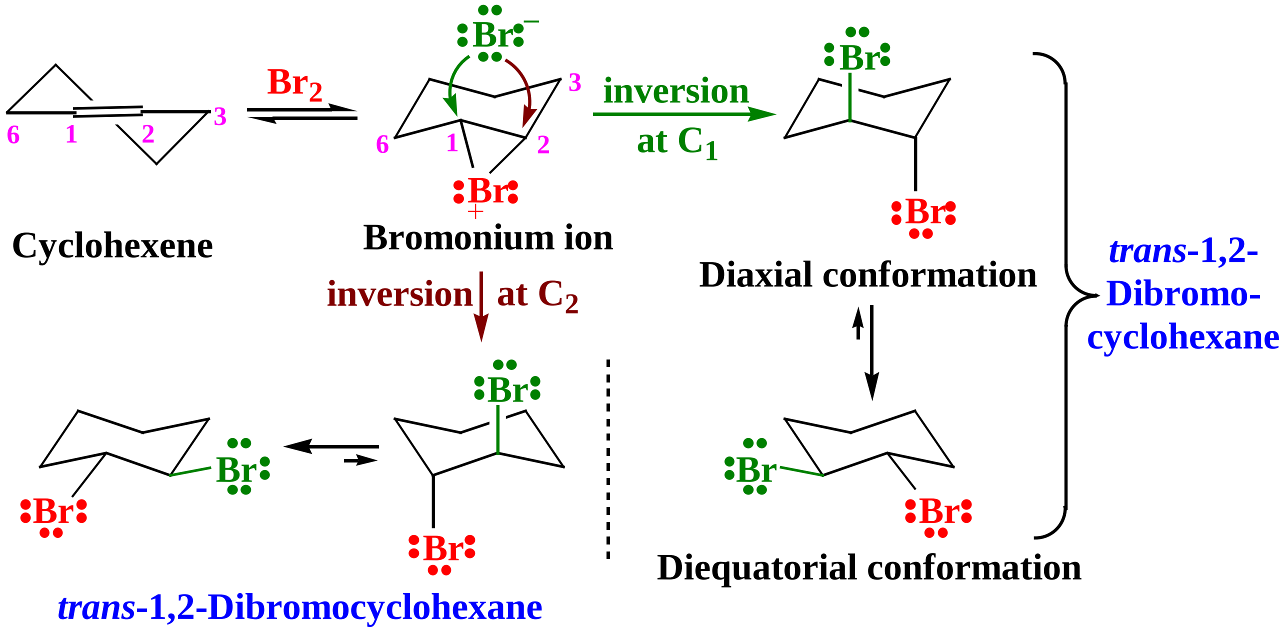
the carbon being attacked which leads to the formation of one enantiomer of *trans*-1,2-dibromocyclopentane.

4) Attack of the bromide ion at the other carbon of the bromonium ion results in the formation of the other enantiomer.





2. **Anti addition** of bromine to cyclohexene:

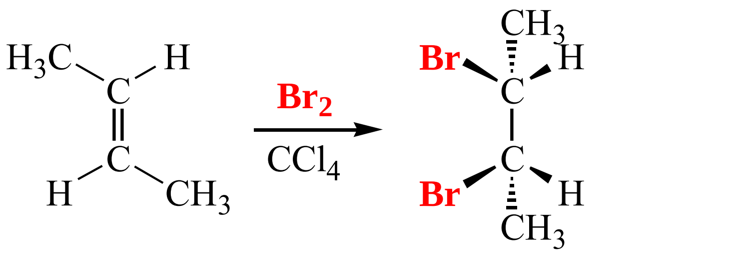


1) The product is a racemate of the *trans*-1,2-dibromocyclohexane.
2) The **initial product** of the reaction is the ***diaxial conformer***.
   i) They rapidly converts to the diequatorial form, and when equilibrium is reached the diequatorial form predominates.
   ii) When cyclohexane derivatives undergo elimination, the required conformation is the diaxial one.

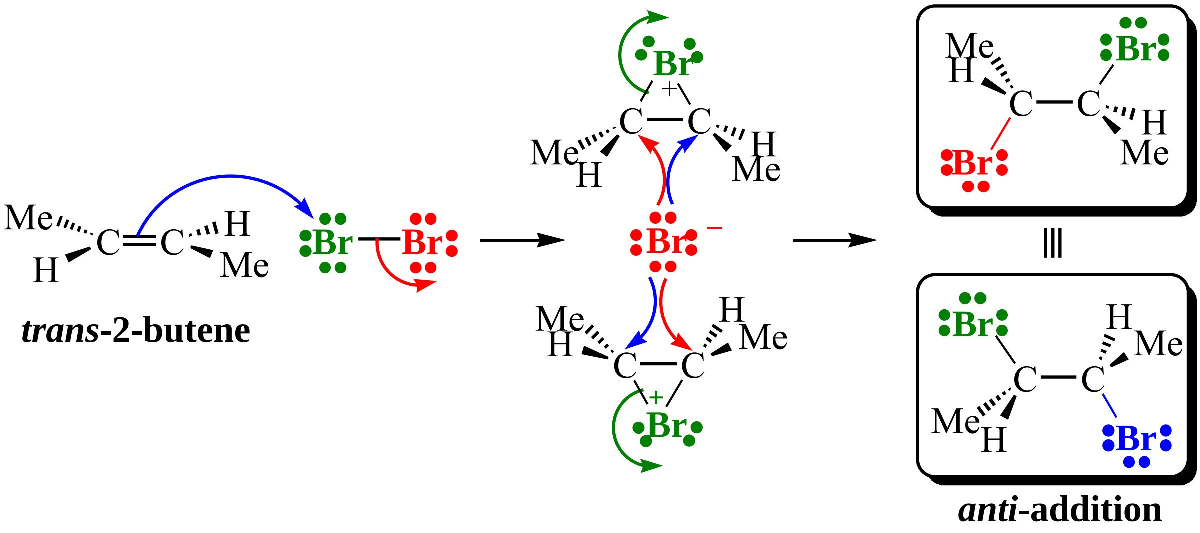
8.7A STEREOSPECIFIC REACTIONS

1. A reaction is ***stereospecific*** when ***a particular stereoisomeric form of the starting material reacts gives a specific stereoisomeric form of the product***.
2. When bromine adds to *trans*-2-butene, the product is (2*R*,3*S*)-2,3-dibromobutane, the meso compound.

Reaction 1

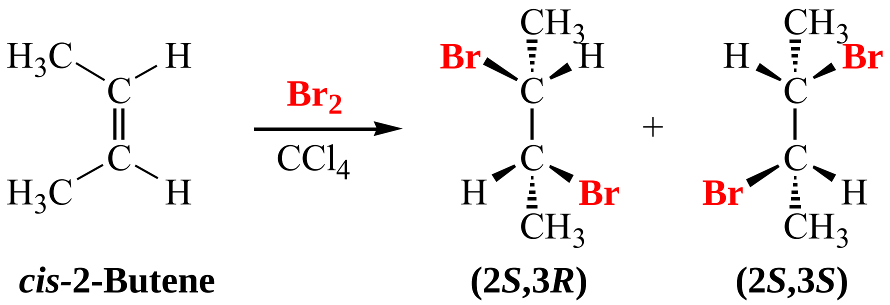


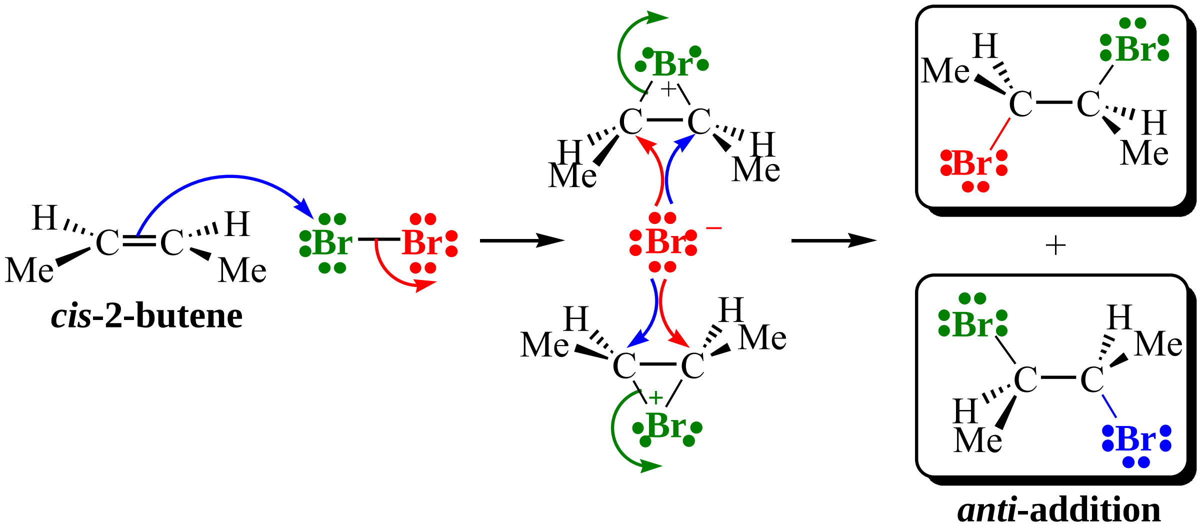
***trans*-2-Butene** **(2*R*,3*S*)-2,3-Dibromobutane (a meso compound)**



3. When bromine adds to *cis*-2-butene, the product is a ***racemic form*** of (2*R*,3*R*)-2,3-dibromobutane and (2*S*,3*S*)-2,3-dibromobutane.

<u>Reaction 2</u>

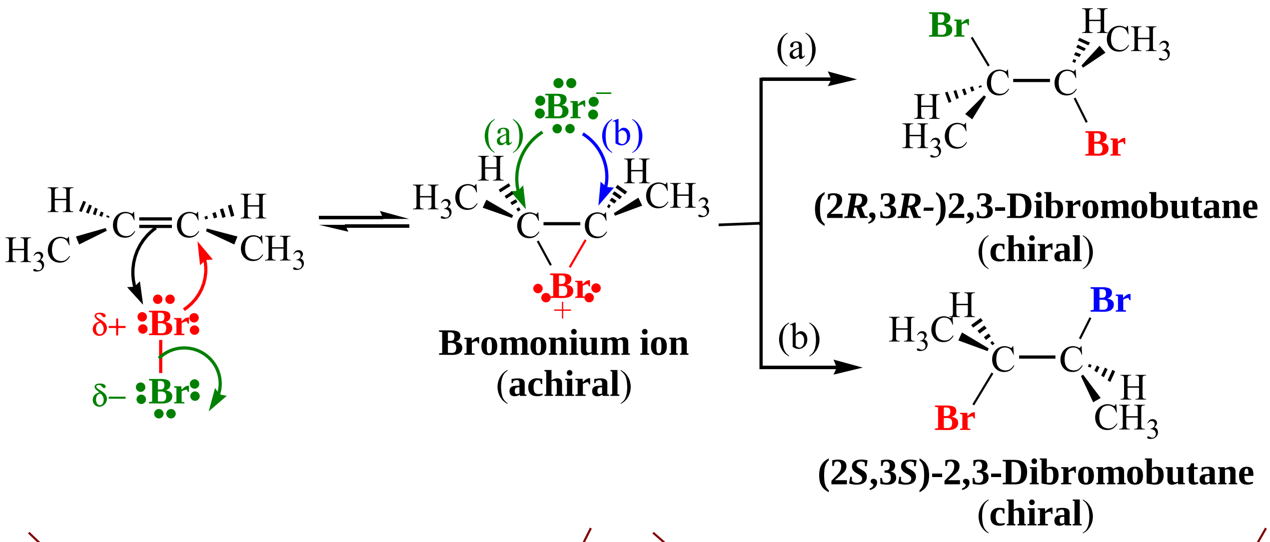




A Stereochemistry of the Reaction

Addition of Bromine to *cis*- and *trans*-2-Butene

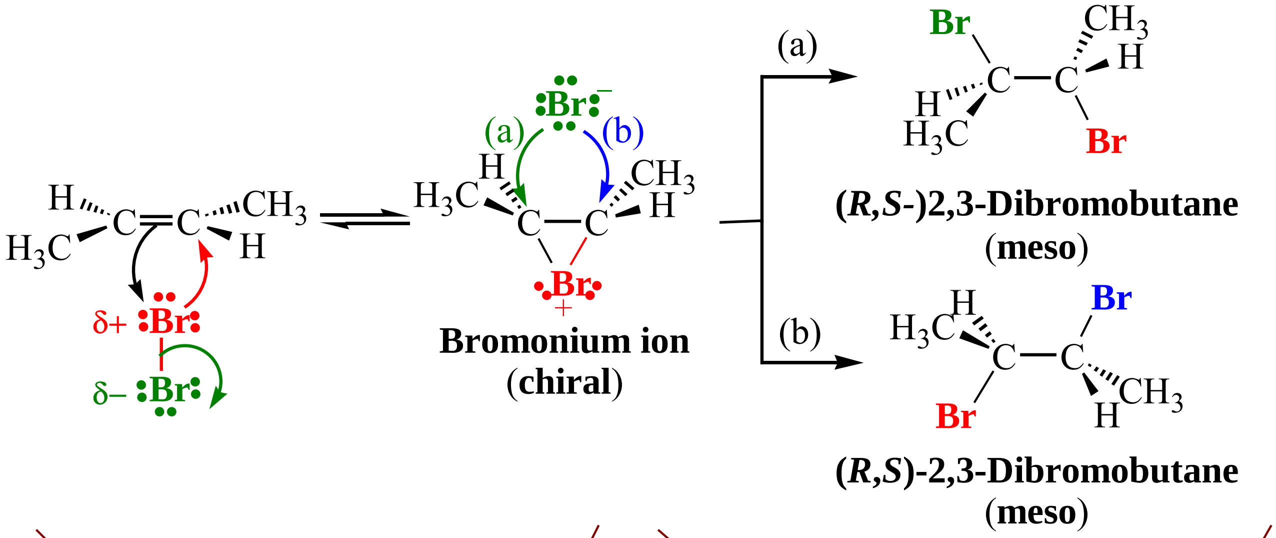
cis-2-Butene reacts with bromine to yield the enantiomeric 2,3-dibromobutanes:



***cis*-2-butene reacts with bromine to yield an achiral bromonium ion and a bromide ion. [Reaction at the other face of the alkene (top) would yield the same bromonium ion.]**

The bromonium ion reacts with the bromide ions at equal rates by paths (a) and (b) to yield the two enantiomers in equal amounts (i.e., as the racemic form).

trans-2-Butene reacts with bromine to yield meso-2,3-dibromobutane.:

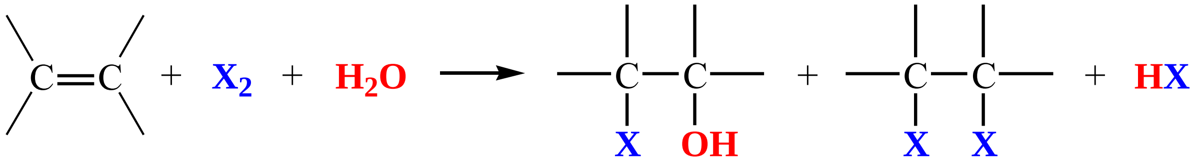


***trans*-2-Butene reacts with bromine yo yield chiral bromonium ions and bromide ions. [Reaction at the other face (top) would yield the enantiomer of the bromonium ion as shown here.]**

When the bromonium ions react by either path (a) or path (b), they yiled the same achiral meso compound. [Reaction of the enantiomer of the intermediate bromonium ion would produce the same result.]

8.8 HALOHYDRIN FORMATION

1. When an alkene is reacted bromine in aqueous solution (rather than CCl_4), the major product is a **halohydrin** (**halo alcohol**).

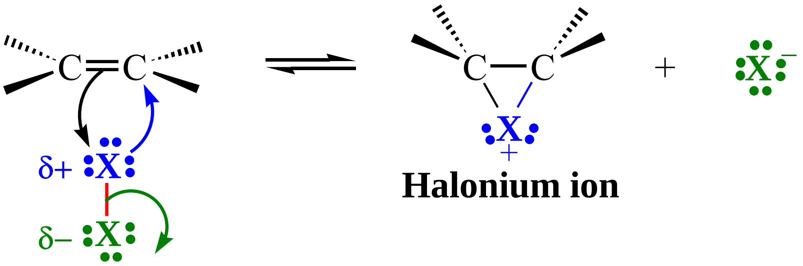


X = Cl or Br | **Halohydrin (major)** | ***vic*-Dihalide (minor)**

A Mechanism for the Reaction

Halohydrin formation from an Alkene

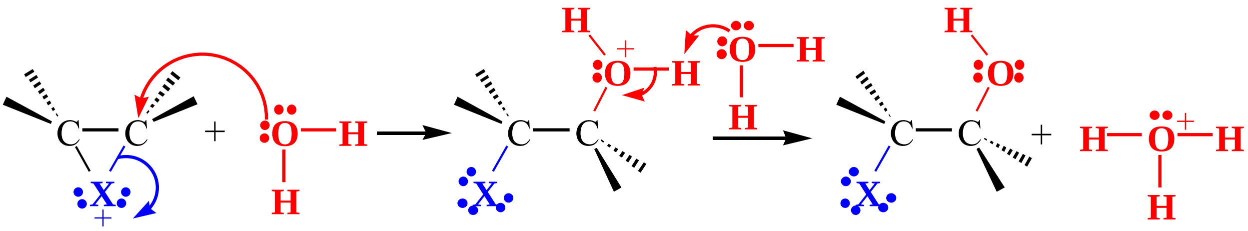
Step 1



Halonium ion

This step is the same as for halogen addition to an alkene

Step 2 and 3



Halonium ion | **Protonated halohydrin** | **Halohydrin**

Here, however, a water molecule acts as the nuclephile and attacks a carbon of the ring, causing the formation of a protonated halohydrin.

The protonated hallohydrin loses a proton (it is transferred to a molecule of water). This step produces the halohydrin and hydronium ion.

1) Water molecules far numbered halide ions because water is the solvent for the

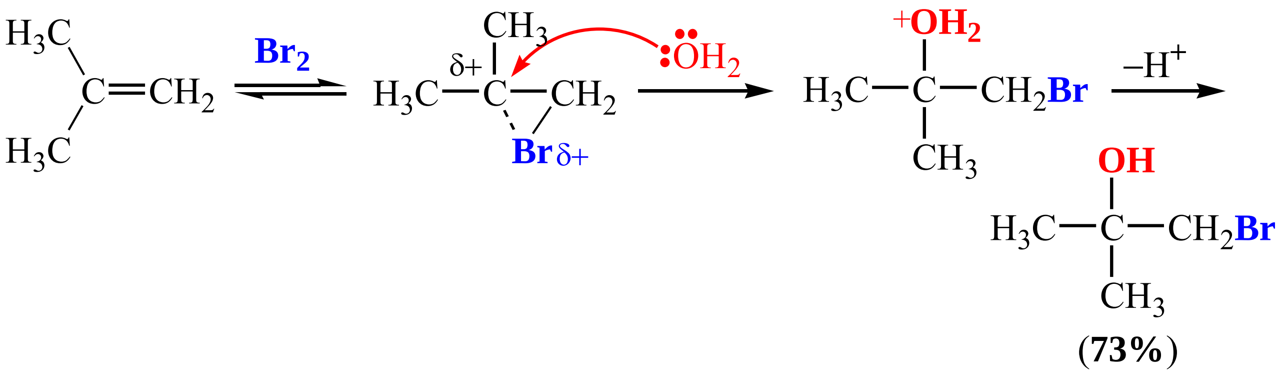
reaction.

2. If the alkene is ***unsymmetrical***, the **halogen** ends up on the **carbon atom** with the ***greater number of hydrogen atoms***.

1) The intermediate bromonium ion is ***unsymmetrical***.

i) The more highly substituted carbon atom bears the greater positive charge because it resembles the more stable carbocation.

ii) Water attacks this carbon atom preferentially.



iii) The greater positive charge on the 3° carbon atom permits a pathway with a lower free energy of activation even though attack at the 1° carbon atom is less hindered.

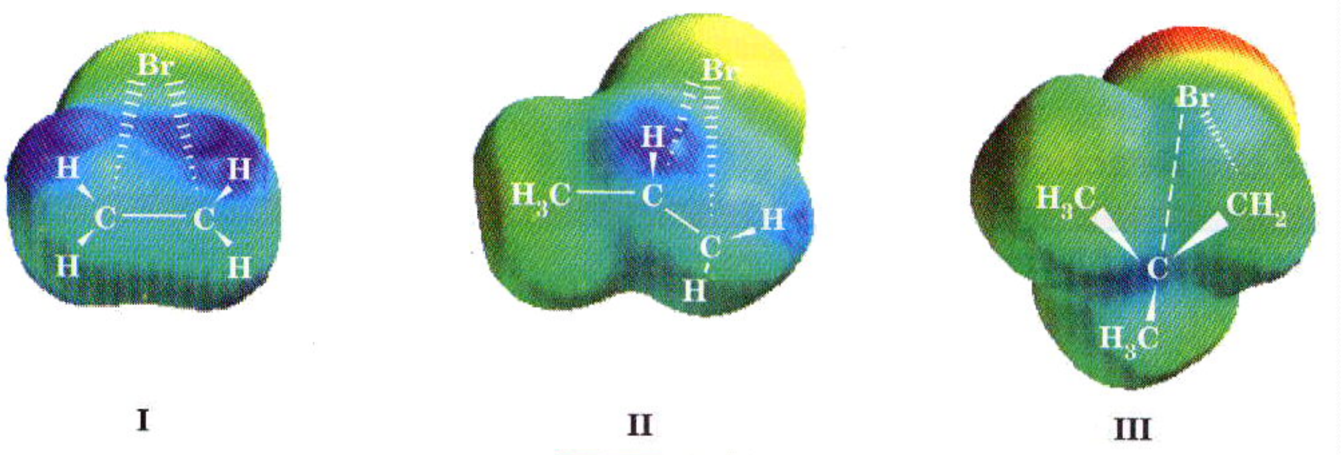
The Chemistry of Regiospecificity in Unsymmetrically Substituted Bromonium Ions: Bromonium Ions of Ethene, Propene, and 2-Methylpropene

1. When a nucleophile reacts with a **bromonium ion**, the addition takes place with **Markovnikov regiochemistry**.

1) In the formation of bromohydrin, bromine bonds at the least substituted carbon (from nucleophilic attack by water), and the hydroxyl group bonds at the more substituted carbon (i.e., the carbon that accommodated more of the positive charge in the bromonium ion).

2. The relative distributions of electron densities in the bromonium ions of ethane,

propene, and 2-methylpropene:



Red indicates relatively negative areas and blue indicates relatively positive (or less negative) areas.

Figure 8.A **As alkyl substitution increases, carbon is able to accommodate greater positive charge and bromine contributes less of its electron density.**

1) As alkyl substitution increases in bromonium ions, the carbon having greater substitution requires less stablization by contribution of electron density from bromine.
2) In the bromonium ion of ethene (**I**), the bromine atom contributes substantial electron density.
3) In the bromonium ion of 2-methylpropene (**III**):
   i) The tertiary carbon can accommodate substantial positive charge, and hence most of the positive charge is localized there (as is indicated by deep blue at the tertiary carbon in the electrostatic potential map).
   ii) The bromine retains the bulk of its electron density (as indicated by the mapping of red color near the bromine).
   ii) The bromonium ion of 2-methylpropene has essentially the charge distribution of a tertiary carbocation at its carbon atoms.
4) The bromonium ion of propene (**II**), which has a secondary carbon, utilizes some electron density from the bromine (as indicated by the moderate extent of yellow near the bromine)

3. Nucleophile reacts with bromonium ions **II** or **III** at the carbon of each that bears the greater positive charge, in accord with Markovnikov regiochemistry.

4. The C–Br bond lengths of bromonium ions **I**, **II**, and **III**:

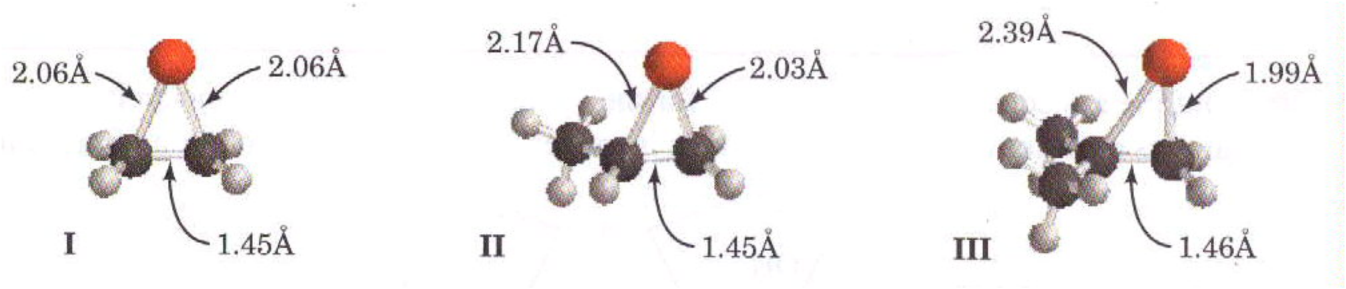


Figure 8.B **The carbon-bromine bond length (shown in angstroms) at the central carbon increases as less electron density from the bromine is needed to stabilize the positive charge. A lesser electron density contribution from bromine is needed because additional alkyl groups help stabilize the charge**

1) In the bromonium ion of ethene (**I**), the C–Br bond lengths are identical (2.06Å).

2) In the bromonium ion of propene (**II**), the C–Br bond involving the 2° carbon is 2.17Å, whereas the one with the 1°carbon is 2.03Å.

   i) The longer bond length to the 2° carbon is consistent with the lesser contribution of electron density from the bromine to the 2° carbon, because the 2° carbon can accommodate the charge better than the 1° carbon.

3) In the bromonium ion of 2-methylpropene (**III**), the C–Br bond involving the 3° carbon is 2.39Å, whereas the one with the 1°carbon is 1.99Å.

   i) The longer bond length to the 3° carbon indicates that significantly less contribution of electron density from the bromine to the 3° carbon, because the 3° carbon can accommodate the charge better than the 1° carbon.

   ii) The bond at the 1° carbon is like that expected for typical alkyl bromide.

5. The lowest unoccupied molecular orbital (LUMO) of ethane, propene, and 2-methylpropene:

1) The lobes of the LUMO on which we should focus on are those opposite the three membered ring portion of the bromonium ion.

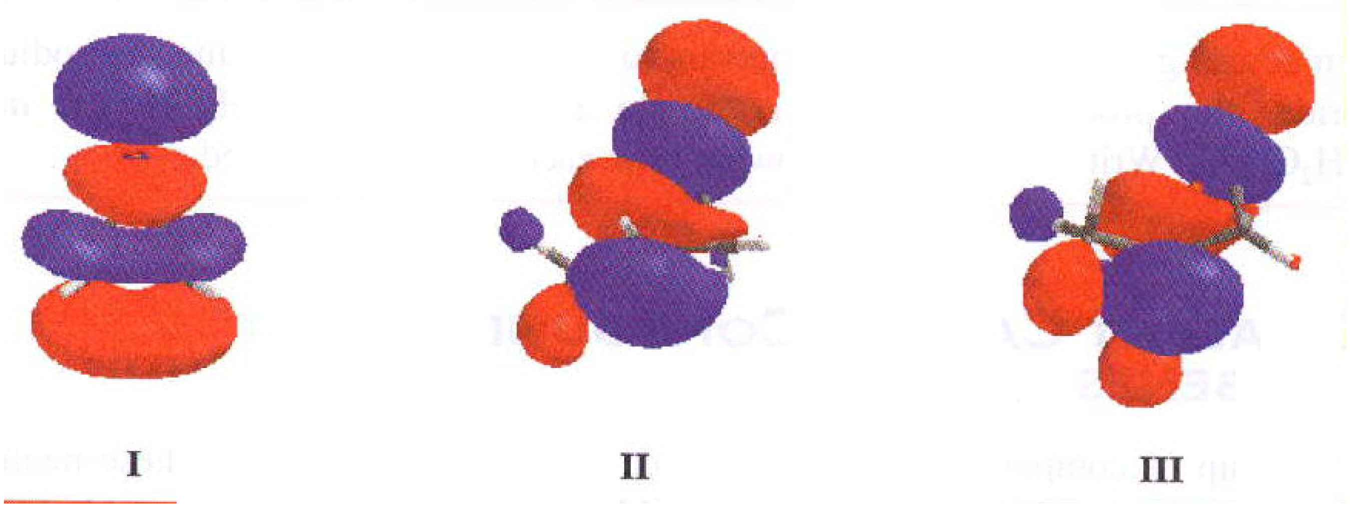


Figure 8.C **With increasing alkyl substitution of the bromonium ion, the lobe of the LUMO where electron density from the nucleophile will be contributed shifts more and more to the more substituted carbon.**

2) In the bromonium ion of ethene (**I**), equal distribution of the LUMO lobe near the two carbons where the nucleophile could attack.

3) In the bromonium ion of propene (**II**), the corresponding LUMO lobe has more of its volume associated with the more substituted carbon, indicating that electron density from the nucleophile will be best accommodated here.

4) In the bromonium ion of 2-methylpropene (**III**) has nearly all of the volume from this lobe of the LUMO associate with the 3° carbon and virtually none associated with the 1° carbon.

8.9 DIVALENT CARBON COMPOUNDS: CARBENES

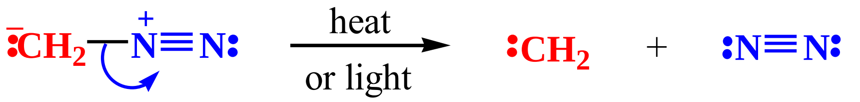
1. **Carbenes:** compounds in which carbon forms only ***two bonds***.

1) Most carbenes are highly unstable compounds that are capable of only fleeting existence.

2) The reactions of carbenes are of great synthetic use in the preparation of compounds that have three-membered rings.

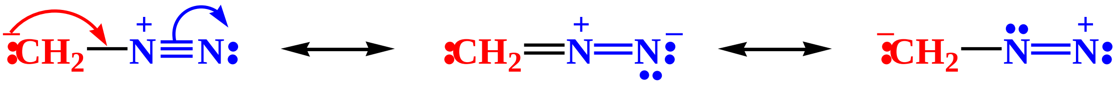
8.9A STRUCTURE AND REACTIONS OF METHYLENE

1. Methylene (:CH_2), the simplest carbene, can be prepared by the decomposition of diazomethane (CH_2N_2).



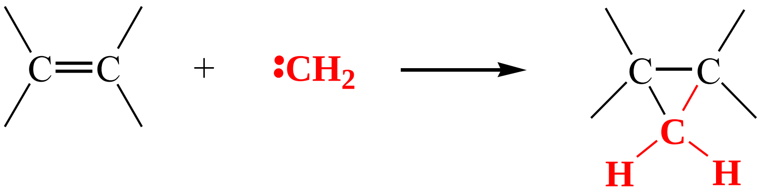
Diazomethane **Methylene** **Nitrogen**

2. The structure of diazomethane is a resonance hybrid of three structures:



I **II** **III**

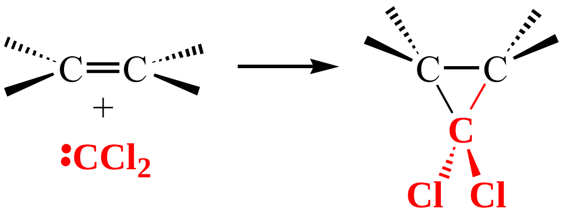
3. Methylene adds to the double bond of alkenes to form cyclopropanes:



Alkene **Methylene** **Cyclopropane**

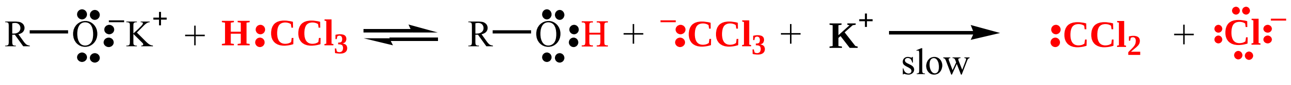
8.9B REACTIONS OF OTHER CARBENES: DIHALOCARBENES

1. Most reactions of dihalocarbenes are stereospecific.



The addition of :CX_2 is stereospecific. If the R groups of the alkene are trans in the product, they will be trans in the product. (If the R groups were initially cis, they would be cis in the product)

2. Dichlorocarbenes can be synthesized by the *α* ***elimination*** of hydrogen chloride from chloroform.

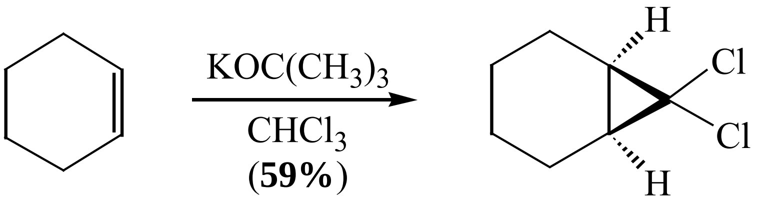


Dichlorocarbene

1) Compounds with a ***β-hydrogen*** react by **β elimination** preferentially.

2) Compounds with no ***β-hydrogen*** but with an ***α-hydrogen*** react by **α elimination**.

3. A variety of cyclopropane derivatives has been prepared by generating dichlorocarbene in the presence of alkenes.



7,7-Dichlorobicyclo[4,1,0]heptane

8.9C CARBENOIDS: THE SIMMONS-SMITH CYCLOPROPANE SYNTHESIS

1. H. E. Simmons and R. D. Smith of the DuPont Company had developed a useful cyclopropane synthesis by reacting a zinc-copper couple with an alkene.

1) The diiodomethane and zinc react to produce a carbene-like species called a ***carbenoid***.

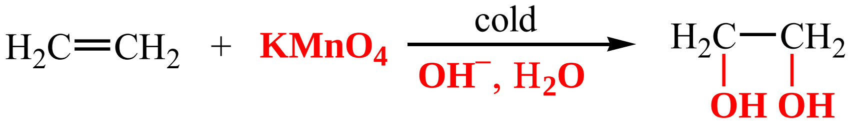
$$CH_2I_2 + Zn(Cu) \longrightarrow ICH_2ZnI$$

A carbeniod

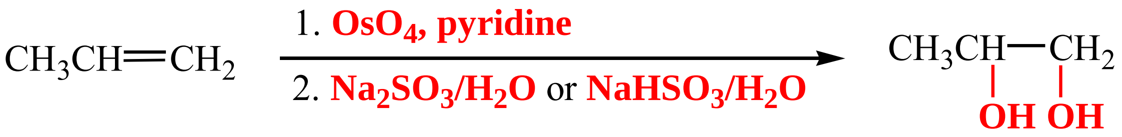
2) The carbenoid then brings about the stereospecific addition of a CH_2 group directly to the double bond.

8.10 OXIDATION OF ALKENES: *SYN*-HYDROXYLATION

1. Potassium permanganate or osmium tetroxide oxidize alkenes to furnish **1,2-diols** (**glycols**).



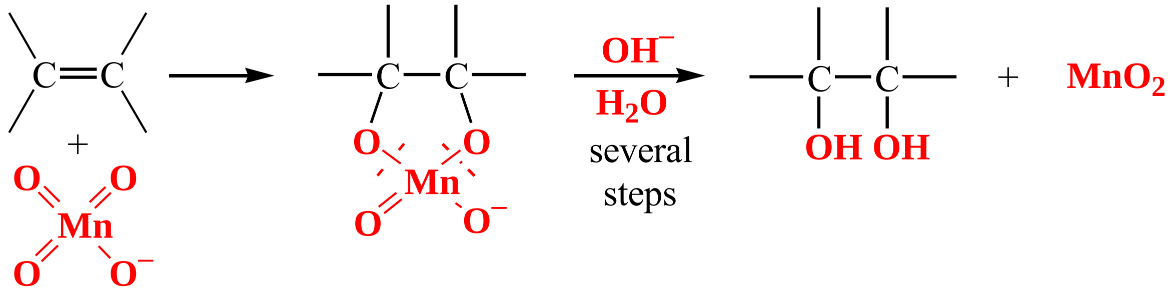
Ethene → **1,2-Ethanediol (ethylene glycol)**

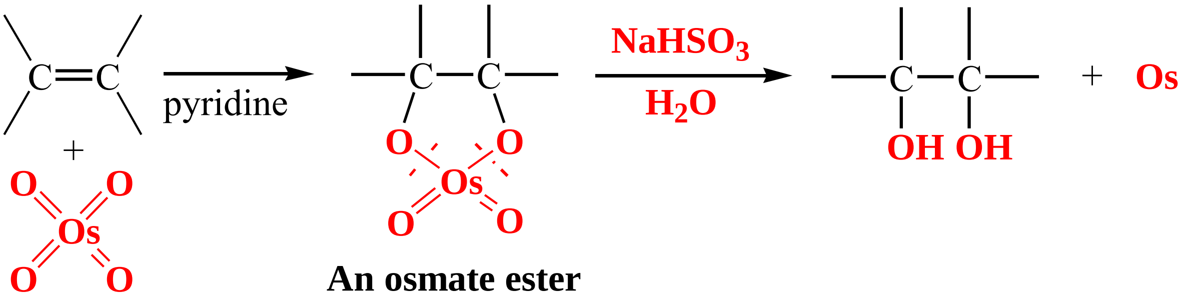


Propene → **1,2-Propaneiol (propylene glycol)**

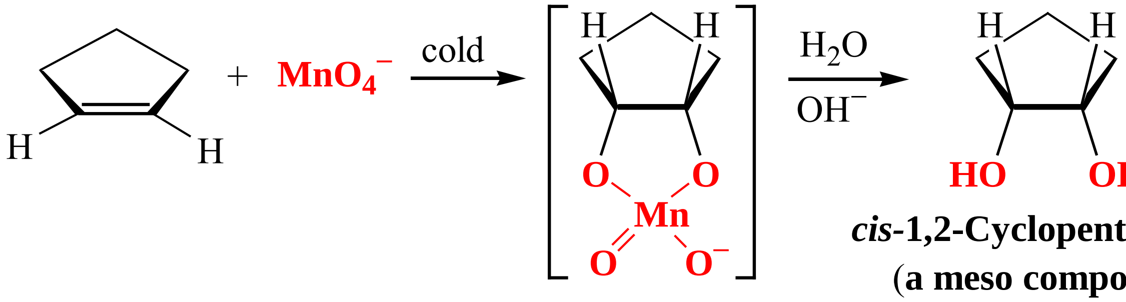
8.10A Mechanisms for *syn*-Hydroxylation of Alkenes

1. The mechanism for the *syn*-hydroxylation of alkenes:

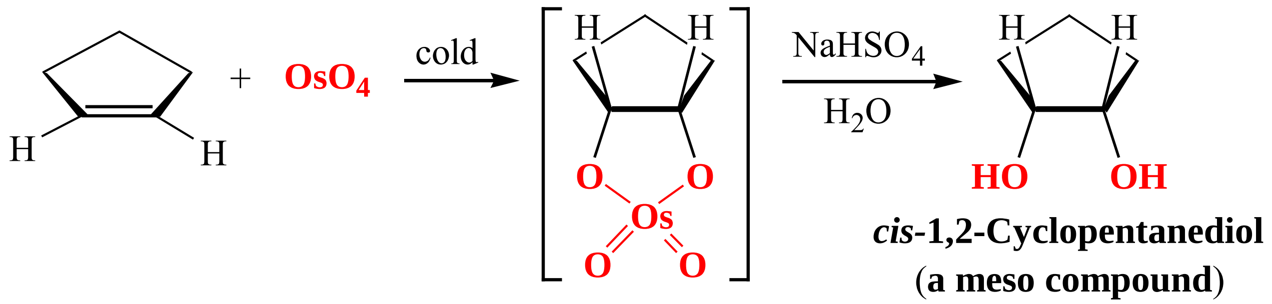




An osmate ester



***cis*-1,2-Cyclopentanediol**
(a meso compound)



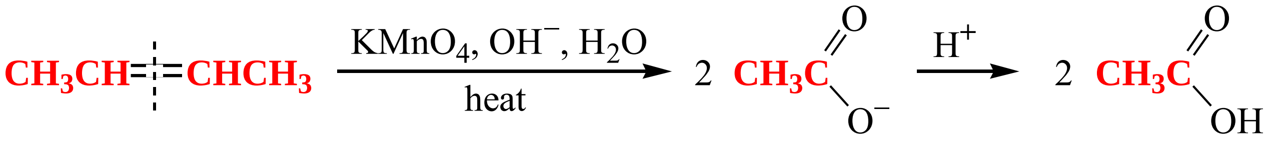
***cis*-1,2-Cyclopentanediol**
(a meso compound)

2. Osmium tetroxide gives the higher yields.
   1) Osmium tetroxide is highly toxic and is very expensive ⇒ Osmium tetroxide is used catalytically in conjunction with a cooxidant.

3. Potassium permanganate is a very powerful oxidizing agent and is ***easily causing further oxidation of the glycol***.
   1) Limiting the reaction to hydroxylation alone is often difficult but usually attempted by using **cold**, **dilute**, and **basic solutions** of potassium permanganate.

8.11 OXIDATIVE CLEAVAGE OF ALKENES

1. Alkenes with monosubstituted carbon atoms are oxidatively cleaved to salts of carboxylic acids ***by hot basic permangnate solutions***.

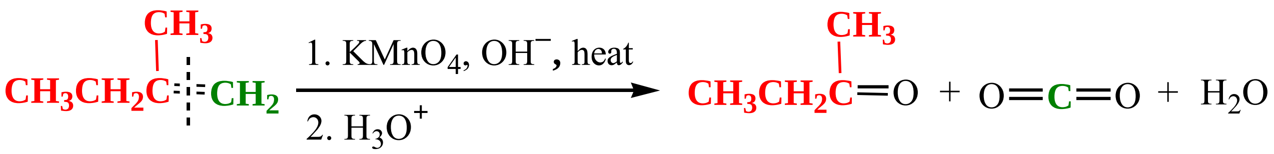


(cis or trans) **Acetate ion** **Acetic acid**

   1) The intermediate in this reaction may be a glycol that is oxidized further with cleavage at the carbon-carbon bond.
   2) Acidification of the mixture, after the oxidation is complete, produces 2 moles of acetic acid for each mole of 2-butene.

2. The terminal CH_2 group of a 1-alkene is completely oxidized to carbon dioxide and water by hot permanganate.
3. A disubstituted carbon atom of a double bond becomes the carbonyl group of a

ketone.



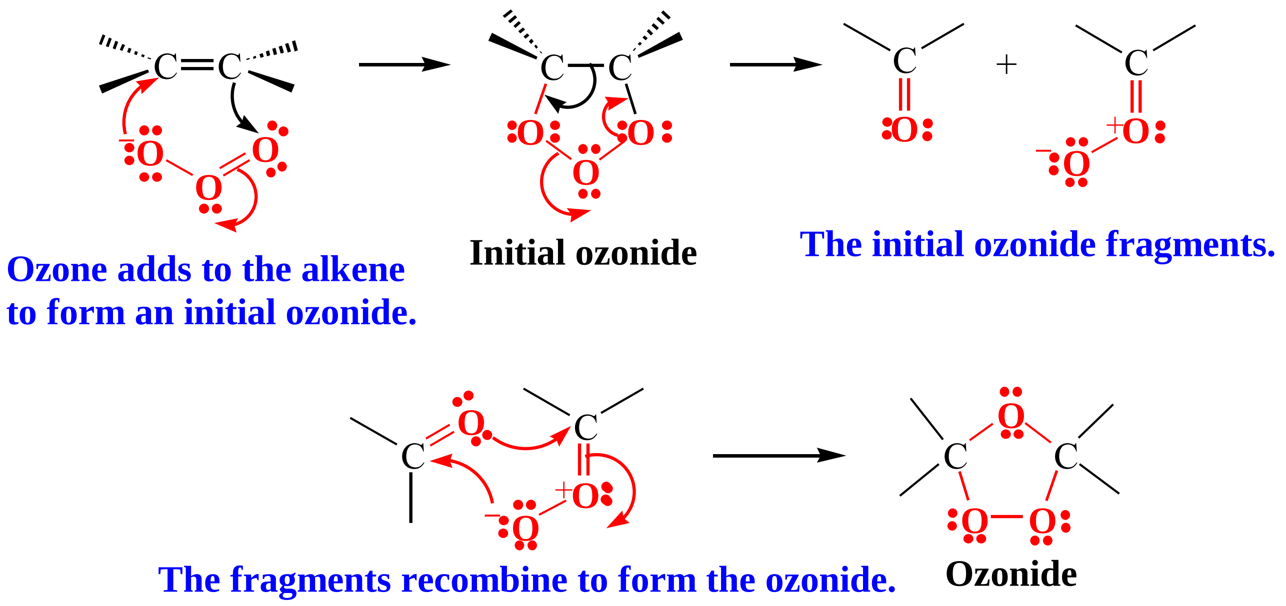
4. The oxidative cleavage of alkenes has been used to establish the location of the double bond in an alkene chain of ring.

8.11A Ozonolysis of Alkenes

1. Ozone reacts vigorously with alkenes to form unstable ***initial ozonides*** (***molozonides***) which rearrange spontaneously to form **ozonides**.
   1) The rearrangement is thought to go through dissociation of the initial ozonide into reactive fragments that recombine to give the ozonide.

A Mechanism for the Reaction

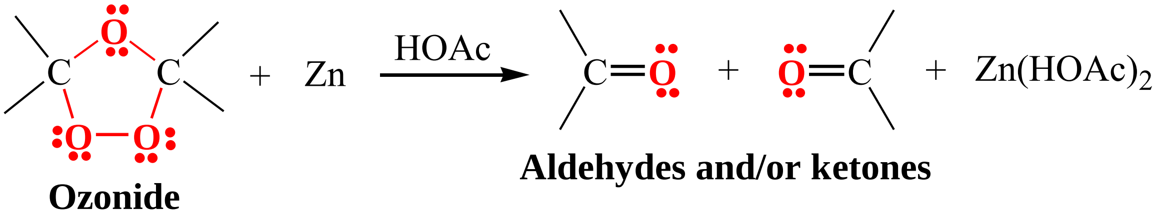
Ozonide Formation from an Alkene



2. Ozonides are very unstable compounds and low molecular weight ononides often explode violently.

1) Ozonides are not usually isolated but are reduced directly by treatment with znic and acetic acid (HOAc).

2) The reduction produces carbonyl compounds (aldehydes or ketones) that can be safely isolated and identified.



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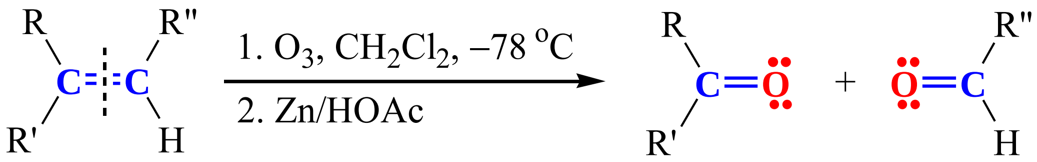
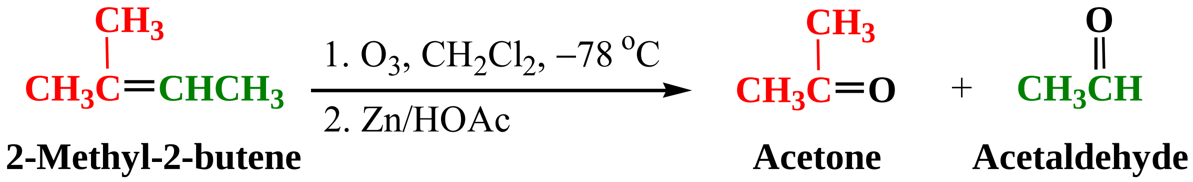
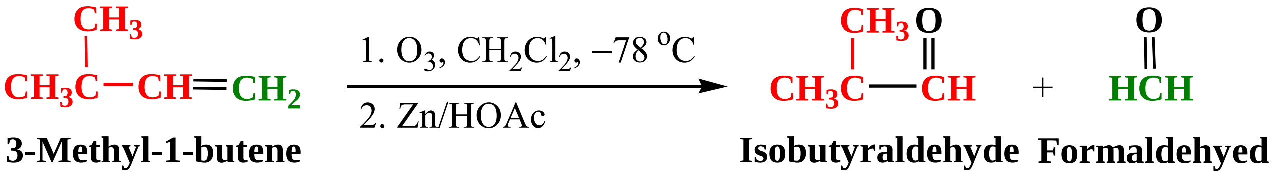
3. The overall process of onzonolysis is:



1) The –H attached to the double bond is not oxidized to –OH as it is with permanganate oxidations

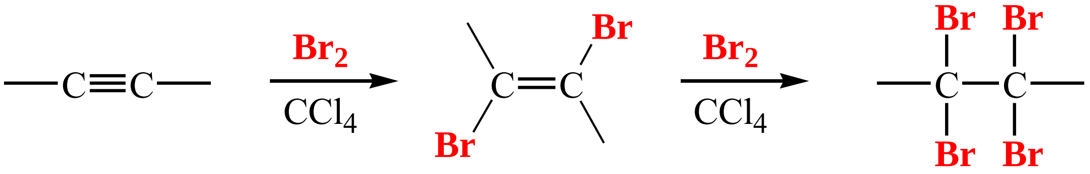




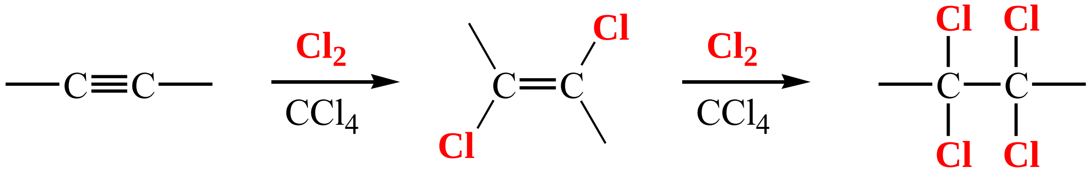
8.12 ADDITION OF BROMINE AND CHLORINE TO ALKYNES

1. Alkynes show the same kind of reactions toward chlorine and bromine that alkenes do: ***They react by addition***.

1) With alkynes, the addition may occur once or twice depending on the number of molar equivalents of halogen employed.



Dibromoalkene Tetrabromoalkane

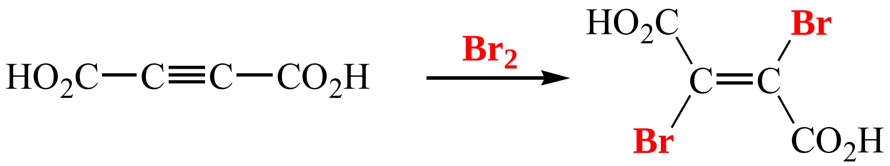


Dichloroalkene Tetrachloroalkane

2. It is usually possible to prepare a dihaloalkene by simply adding one molar equivalent of the halogen.

$$H_3CH_2CH_2CH_2CC{\equiv}CCH_2OH \xrightarrow[CCl_4,\ 0^{o}C]{Br_2\ (1\ mol)} CH_3CH_2CH_2CH_2CBr{=}CBrCH_2OH \quad (80\%)$$

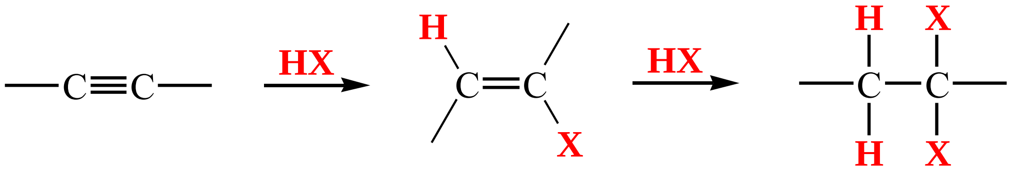
3. Most additions of chlorine and bromine to alkynes are anti additions and yield *trans*-dihaloalkenes.



Acetylenedicarboxylic acid (70%)

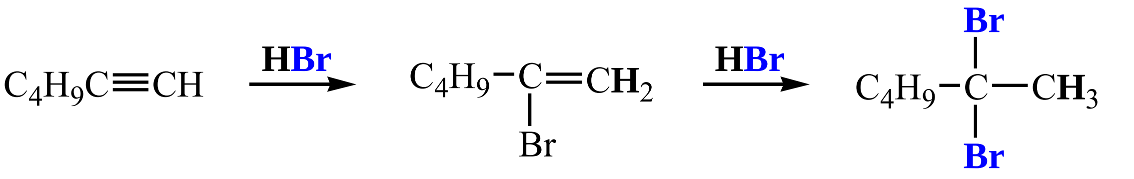
8.13 ADDITION OF HYDROGEN HALIDES TO ALKYNES

1. Alkynes react with HCl and HBr to form haloalkenes or geminal dihalides depending on whether one or two molar equivalents of the hydrogen halide are used.
   1) Both additions are **regioselective** and follow **Markovnikov's rule:**



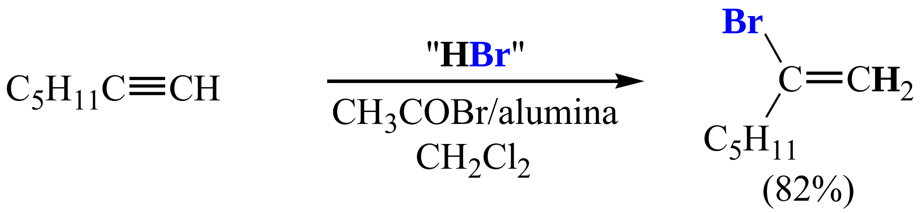
Haloalkene ***gem*-Dihalide**

2) The H atom of the HX becomes attached to the carbon atom that has the greater number of H atoms.

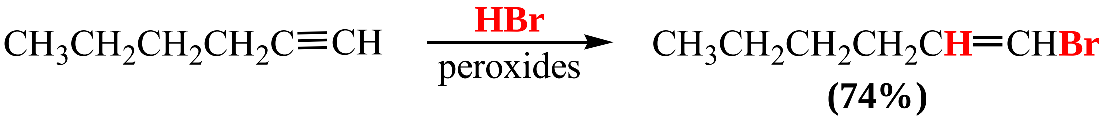


2-Bromo-1-hexene **2,2-Dibromohexane**

2. The addition of HBr to an alkyne can be facilitated by using acetyl bromide (CH_3COBr) and alumina instead of aqueous HBr.
   1) CH_3COBr acts as an HBr precursor by reacting with alumina to generate HBr.
   2) The alumina increases the rate of reaction.



3. Anti-Markovnikov addition of HBr to alkynes occur when peroxides are present.
   1) These reactions take place through a free radical mechanism.



8.14 Oxidative Cleavage of Alkynes

1. Treating alkynes with ozone or with basic potassium permanganate leads to

cleavage at the C≡C.

$$R{-}C{\equiv}C{-}R' \xrightarrow[\text{2. HOAc}]{\text{1. } O_3} RCO_2H + R'CO_2H$$

$$R{-}C{\equiv}C{-}R' \xrightarrow[\text{2. } H^+]{\text{1. } KMnO_4,\ OH^-} RCO_2H + R'CO_2H$$

8.15 SYNTHETIC STRATEGIES REVISITED

1. Four interrelated aspects to be considered in planning a synthesis:
   1) Construction of the carbon skeleton.
   2) Functional group interconversion.
   3) Control of **regiochemistry**.
   4) Control of **stereochemistry**.

2. Synthesis of 2-bromobutane from compounds of two carbon atoms or fewer:

   Retrosynthetic Analysis

$$CH_3CH_2CH(Br)CH_3 \Rightarrow CH_3CH_2CH{=}CH_2 + H{-}Br$$ **Markovnikov addition**

   Synthesis

$$CH_3CH_2CH{=}CH_2 + H{-}Br \xrightarrow[\text{peroxide}]{\text{no}} CH_3CH_2CH(Br)CH_3$$

Target molecule $\Rightarrow$ **Precursor**

3. Synthesis of 1-butene from compounds of two carbon atoms or fewer:

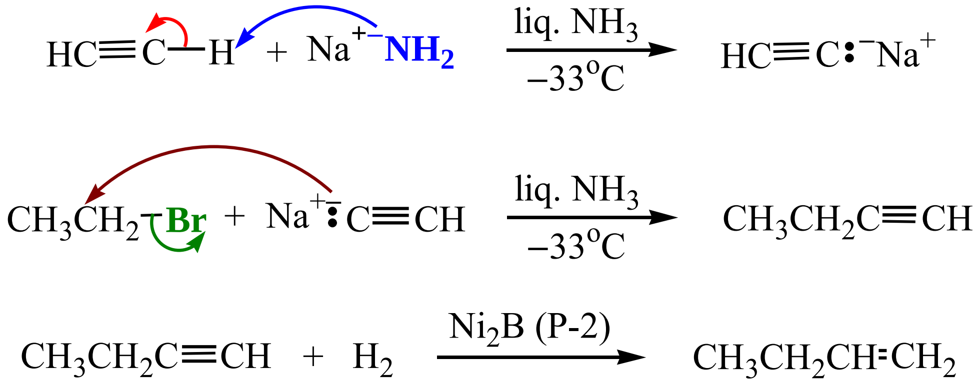
   Retrosynthetic Analysis

$$CH_3CH_2CH{=}CH_2 \Rightarrow CH_3CH_2C{\equiv}CH + H_2$$

$$CH_3CH_2C{\equiv}CH \Rightarrow CH_3CH_2Br + NaC{\equiv}CH$$

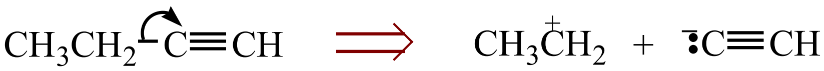
$$NaC{\equiv}CH \Longrightarrow HC{\equiv}CH + NaNH_2$$

Synthesis



4. Disconnection:

1) Warren, S. "*Organic Synthesis, The Disconnection Approach*"; Wiley: New York, **1982**. Warren, S. "*Workbook for Organic Synthesis, The Disconnection Approach*"; Wiley: New York, **1982**.



i) The fragments of this disconnection are an ethyl cation and an ethynide anion.

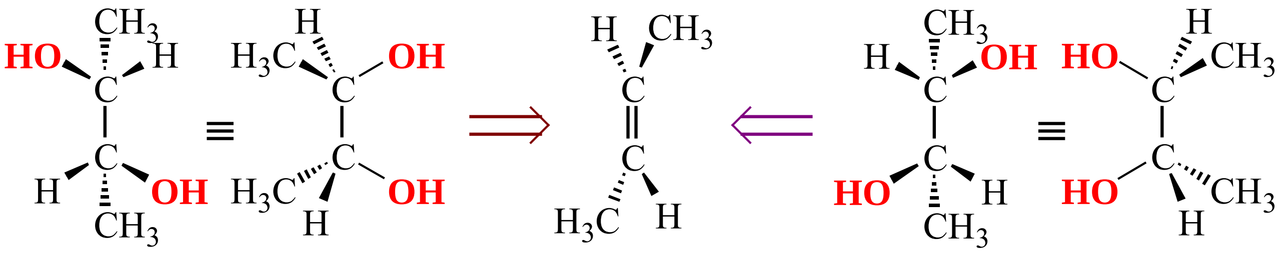
ii) These fragments are called **synthons** (**synthetic equivalents**).

$$CH_3\overset{+}{C}H_2 \equiv CH_3CH_2Br \qquad {}^{-}{:}C{\equiv}CH \equiv Na^{+}\,{}^{-}{:}C{\equiv}CH$$

5. Synthesis of (2*R*,3*R*)-2,3-butanediol and (2*S*,3*S*)-2,3-butanediol from compounds of two carbon atoms or fewer:

1) Synthesis of 2,3-butanediol enantiomers: ***syn*-hydroxylation of *trans*-2-butene**.

Retrosynthetic Analysis



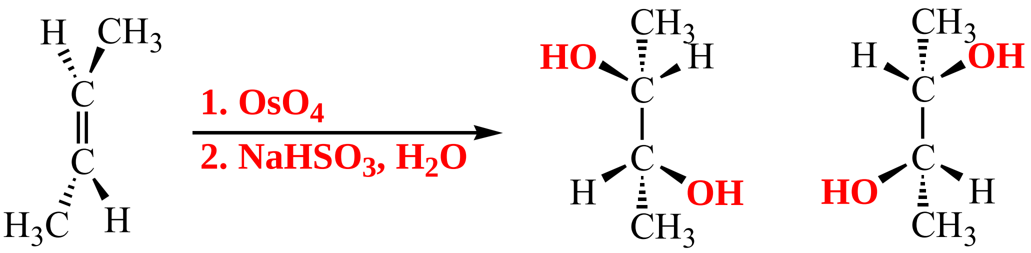
(*R*,*R*)-2,3-butanediol

trans-2-Butene

syn-hydroxylation
at either face of the alkene

(*S*,*S*)-2,3-butanediol

Synthesis



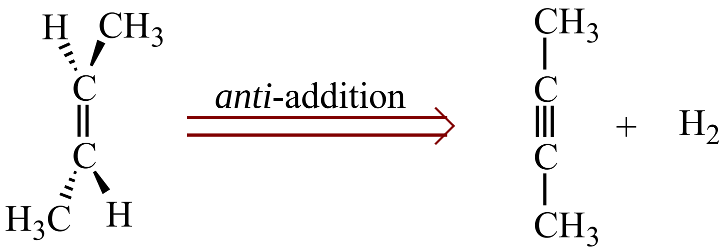
trans-2-Butene

(*R*,*R*) (*S*,*S*)
Enantiomeric 2,3-butanediols

i) This reaction is stereospecific and produces the desired enantiomeric 2,3-butanediols as a racemic mixture (racemate).

2) Synthesis of *trans*-2-butene:

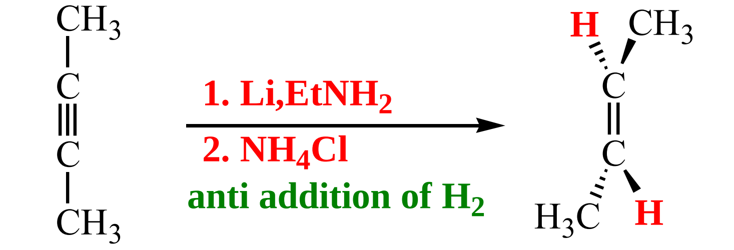
Retrosynthetic Analysis



trans-2-Butene

2-Butyne

Synthesis



2-Butyne **_trans_-2-Butene**

3) Synthesis of 2-butyne:

Retrosynthetic Analysis

$$H_3C-C\equiv C\text{-}\wr\text{-}CH_3 \Longrightarrow H_3C-C\equiv C{:}^{-}Na^{+} + CH_3-I$$

$$H_3C-C\equiv C{:}^{-}Na^{+} \longrightarrow H_3C-C\equiv C-H + NaNH_2$$

Synthesis

$$H_3C-C\equiv C-H \xrightarrow[\text{2. } CH_3I]{\text{1. } NaNH_2/\text{liq. } NH_3} H_3C-C\equiv C-CH_3$$

4) Synthesis of propyne:

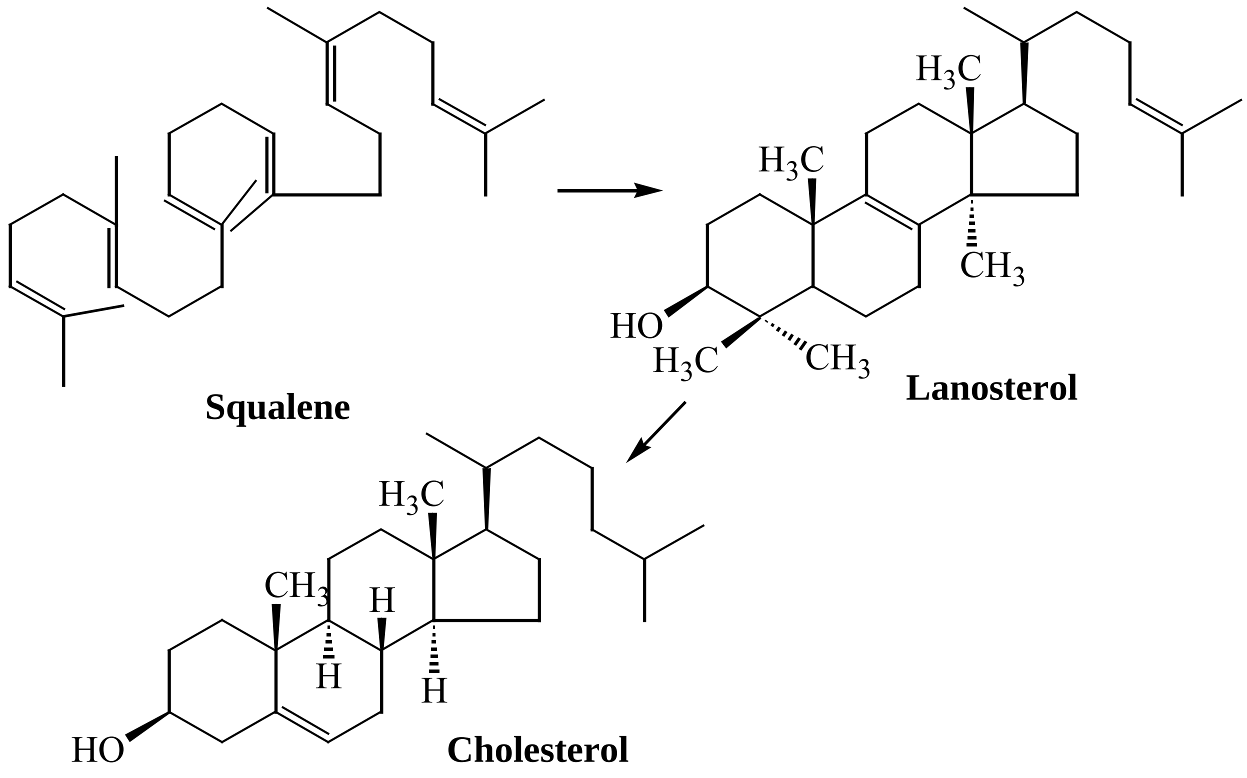
Retrosynthetic Analysis

$$H-C\equiv C\text{-}\wr\text{-}CH_3 \Longrightarrow H-C\equiv C{:}^{-}Na^{+} + CH_3-I$$

Synthesis

$$H-C\equiv C-H \xrightarrow[\text{2. } CH_3I]{\text{1. } NaNH_2/\text{liq. } NH_3} H-C\equiv C-CH_3$$

The Chemistry of Cholesterol Biosynthesis: Elegant and Familiar Reactions in Nature



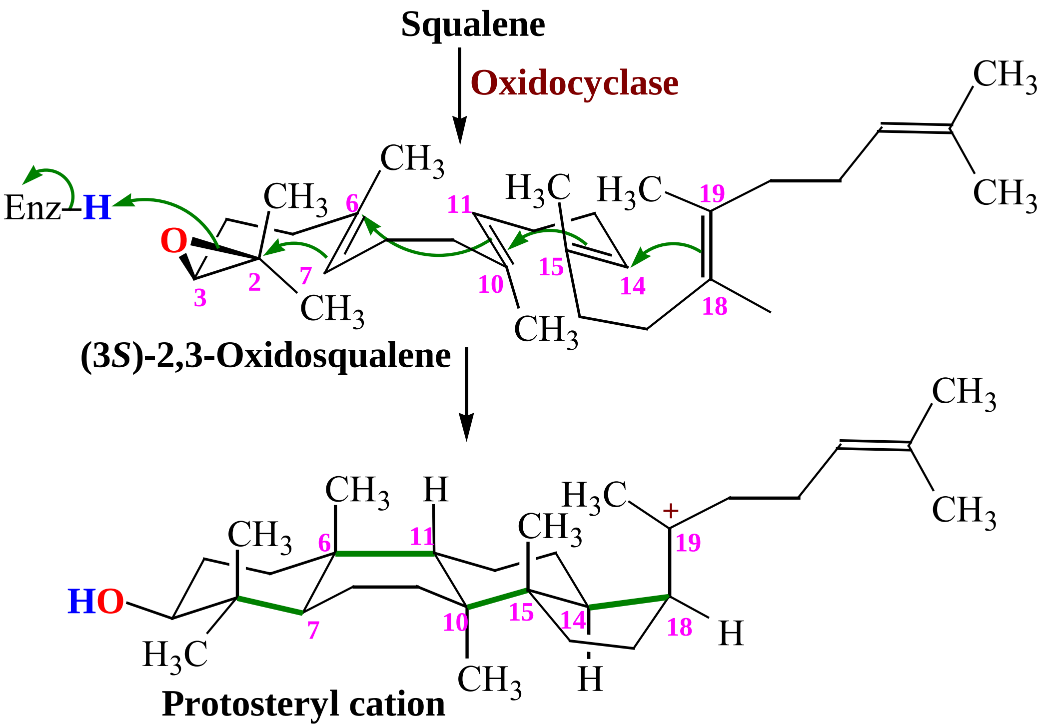
1. Cholesterol is the biochemical precursor of cortisone, estradiol, and testosterone.
   1) Cholesterol is the parent of all of the steroid hormones and bile acids in the body.

2. The last acyclic precursor of cholesterol biosynthesis is **squalene**, consisting of a linear polyalkene chain of 30 carbons.

3. From squalene, **lanosterol**, the first cyclic precursor, is created by a remarkable set of enzyme-catalyzed addition reactions and rearrangements that create four fused rings and seven stereocenters.
   1) In theory, 2^7 (or 128) stereoisomers are possible.

4. **Polyene Cyclization of Squalene to Lanosterol**
   1) The sequence of transformations from squalene to lanosterol begins by the enzymatic oxidation of the 2,3-double bond of squalene to form (3*S*)-2,3-oxidosqualene [also called squalene 2,3-epoxide].
   2) A cascade of alkene addition reactions begin through a **chair-boat-chair** conformation transition state.
      i) Protonation of (3*S*)-2,3-oxidosqualene by squalene oxidocyclase gives the oxygen a formal positive charge and converts it to a good leaving group.

ii) Protonation of (3*S*)-2,3-oxidosqualene by squalene oxidocyclase gives the oxygen a formal positive charge and converts it to a good leaving group.



iii) The protonated epoxide makes the tertiary carbon (C2) electron deficient (resembling a 3° carbocation), and C2 serves as the electrophile for an addition with the double bond between C6 and C7 in the squalene chain ⇒ another 3° carbocation begins to develop at C6.

iv) The C6 carbocation is attacked by the next double bond, and so on for two more alkene additions until the exocyclic tertiary **proteosteryl cation** results.

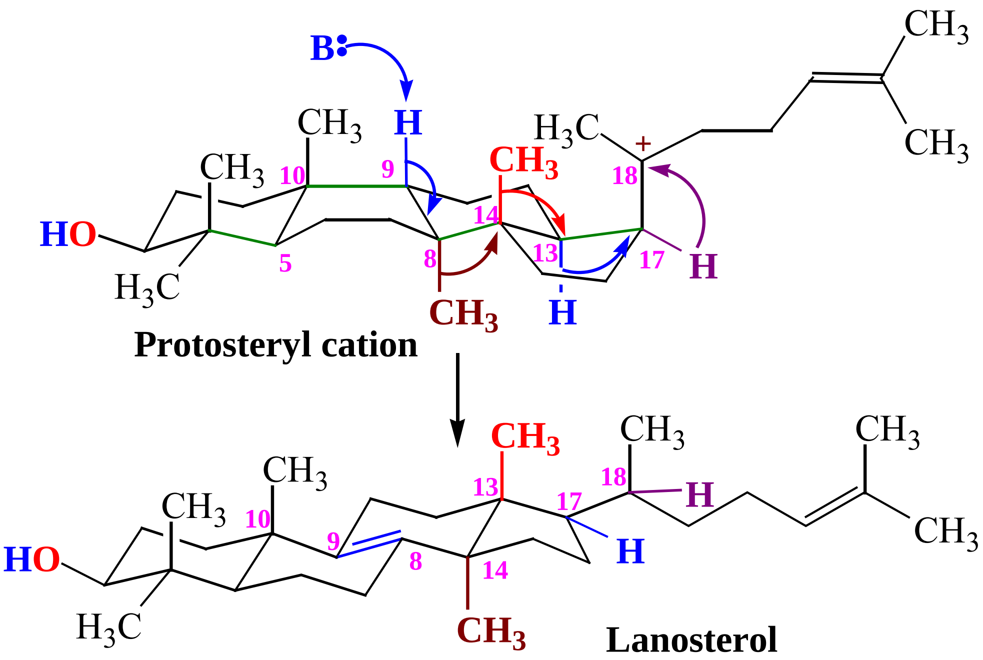
4. **An Elimination Reaction Involving a Sequence of 1,2-Methanide and 1,2-Hydride Rearrangements**

1) The subsequent transformations involved a series of migrations (carbocation rearrangements) followed by removal of a proton to form an alkene.

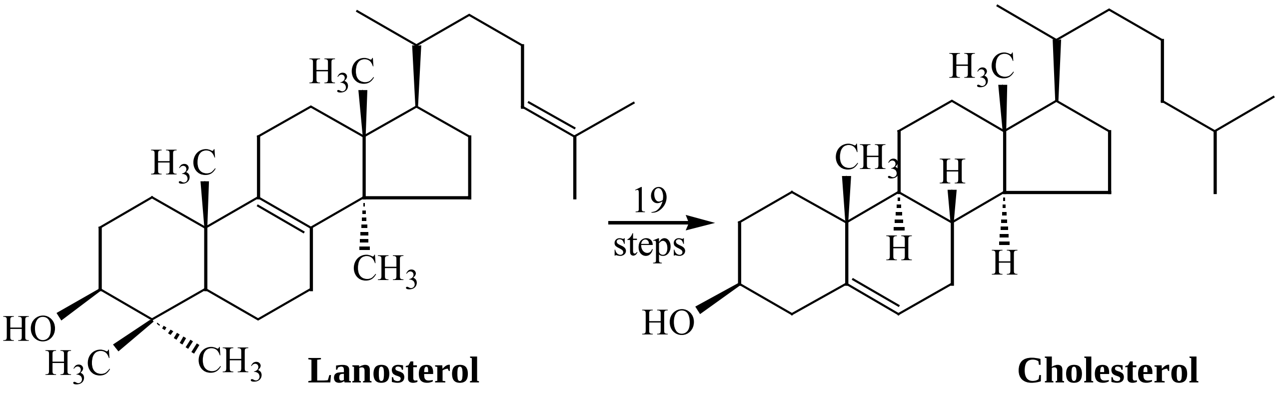
i) The process begins with a 1,2-hydride shift from C17 to C18, leading to development of positive charge at C17.

ii) The developing positive charge at C17 facilitates another hydride shift from C13 to C17 which is accompanied by methyl shift from C14 to C13 and C8 to C14.

iii) Finally, enzymatic removal of a proton from C9 forms the C8-C9 double bond leading to lanosterol.



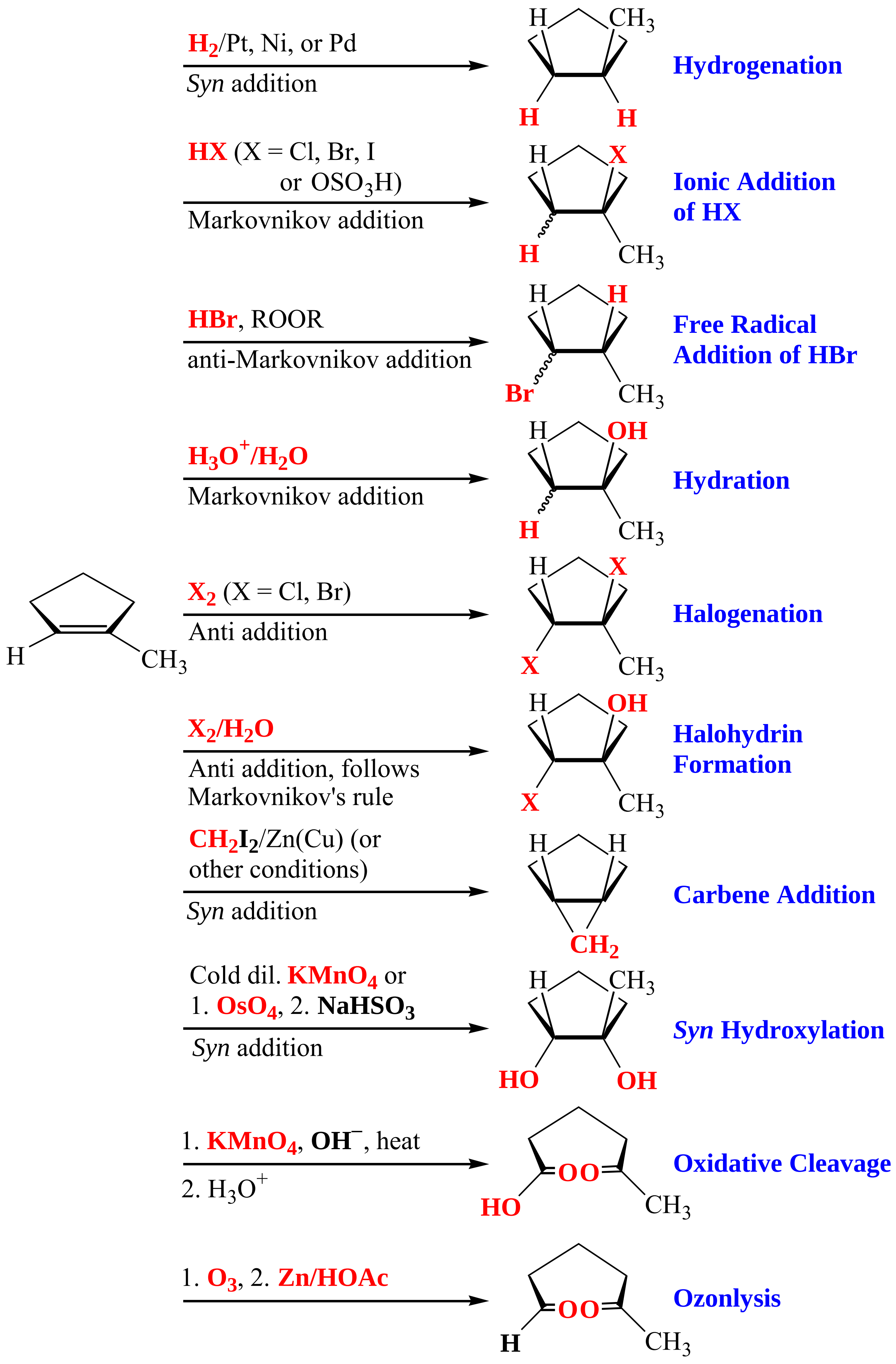
5. The remaining steps to cholesterol involve loss of three carbons through 19 oxidation-reduction steps:



6. Biosynthetic reactions occur on the basis of the same fundamental principles and reaction pathways in organic chemistry.

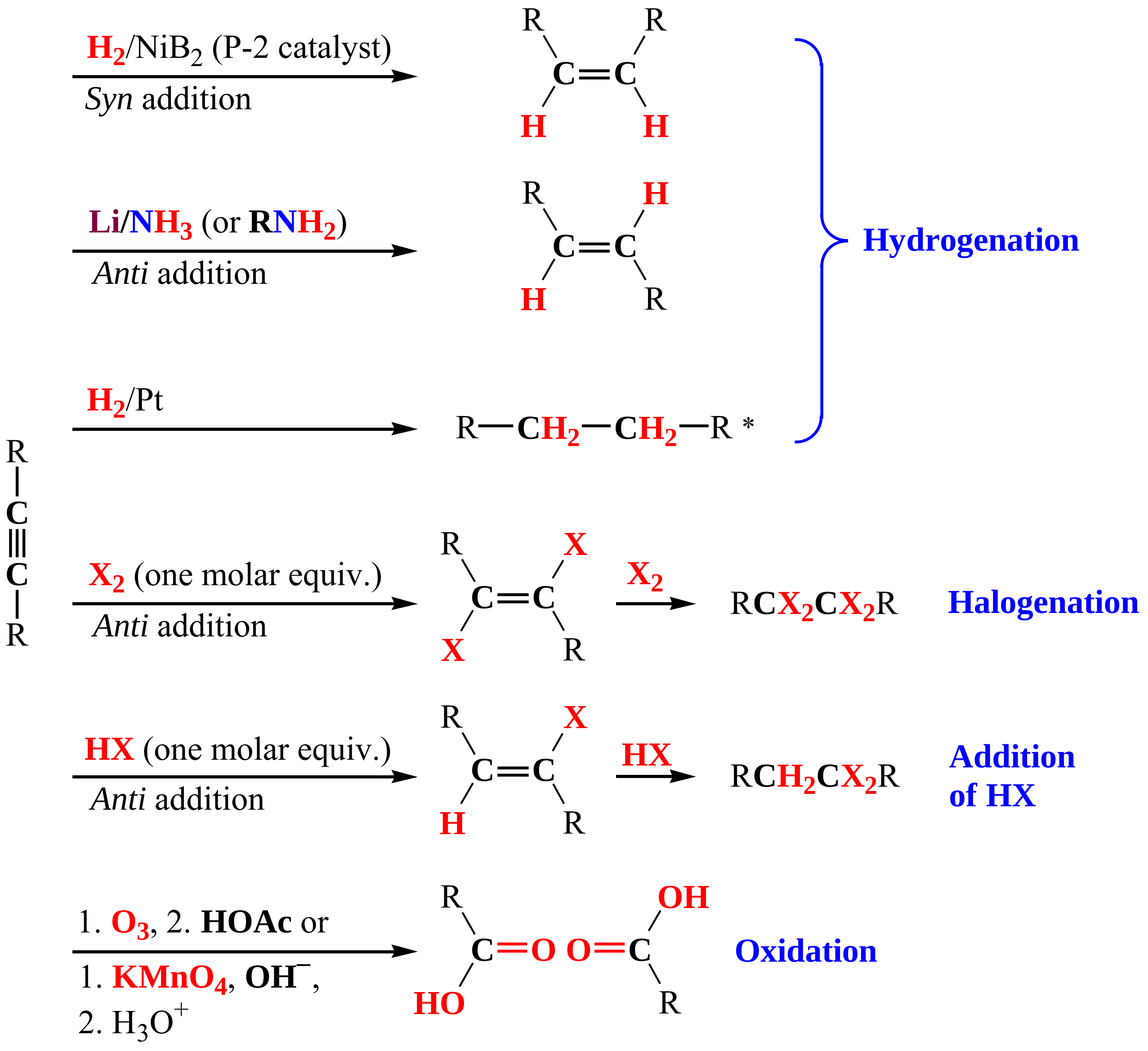
8.16 SUMMARY OF KEY REACTIONS

Summary of Addition Reactions of Alkenes


H2/Pt, Ni, or Pd
Syn addition
Hydrogenation
HX (X = Cl, Br, I
or OSO3H)
Markovnikov addition
Ionic Addition
of HX
HBr, ROOR
anti-Markovnikov addition
Free Radical
Addition of HBr
H3O+/H2O
Markovnikov addition
Hydration
X2 (X = Cl, Br)
Anti addition
Halogenation
X2/H2O
Anti addition, follows
Markovnikov's rule
Halohydrin
Formation
CH2I2/Zn(Cu) (or
other conditions)
Syn addition
Carbene Addition
Cold dil. KMnO4 or
1. OsO4, 2. NaHSO3
Syn addition
Syn Hydroxylation
1. KMnO4, OH−, heat
2. H3O+
Oxidative Cleavage
1. O3, 2. Zn/HOAc
Ozonlysis

A summary of addition reactions of alkenes with 1-methylcyclopentene as the organic substrate. A bond designated 〰〰 means that the stereochemistry of the group is unspecified. For brevity the structure of only one enantiomer of the product is shown, even though racemic mixtures would be produced in all instances in which the product is chiral.

Summary of Addition Reactions of Alkynes

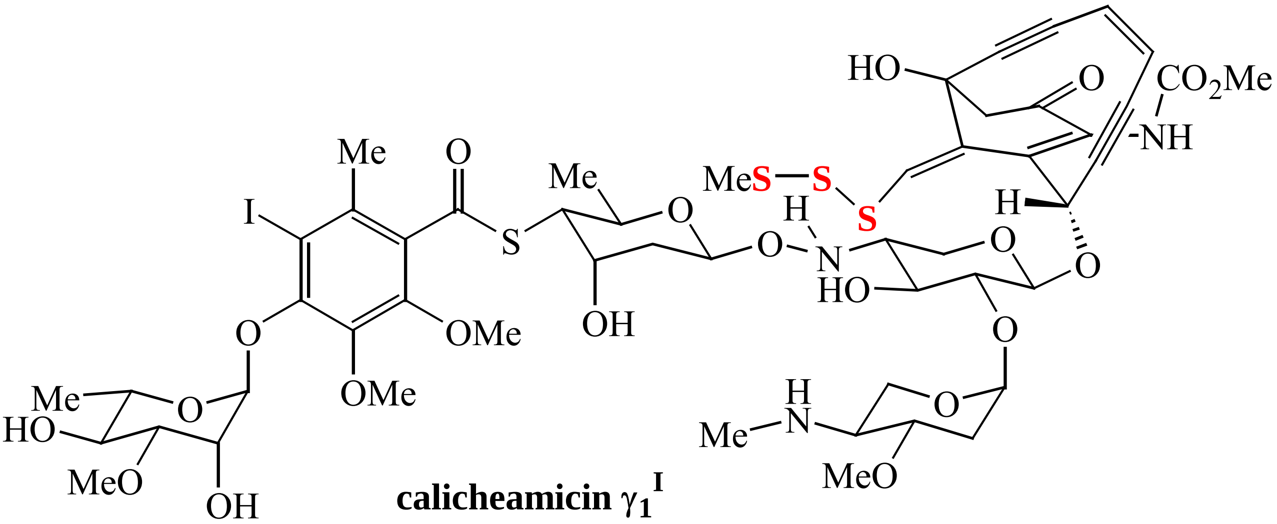


Radical Reactions

Calicheamicin γ_1^I: A Radical Device for Slicing the Backbone of DNA

1. Calicheamicin γ_1^I binds to the minor groove of DNA where its unusual enediyne moiety reacts to form a highly effective device for slicing the backbone of DNA.
   1) Calicheamicin γ_1^I and its analogs are of great clinical interest because they are extraordinarily deadly for tumor cells.
   2) They have been shown to initiate apoptosis (programmed cell death).

2. Bacteria called ***Micromonospora echinospora*** produce calicheamicin γ_1^I as a natural metabolite, presumably as a chemical defense against other organisms.

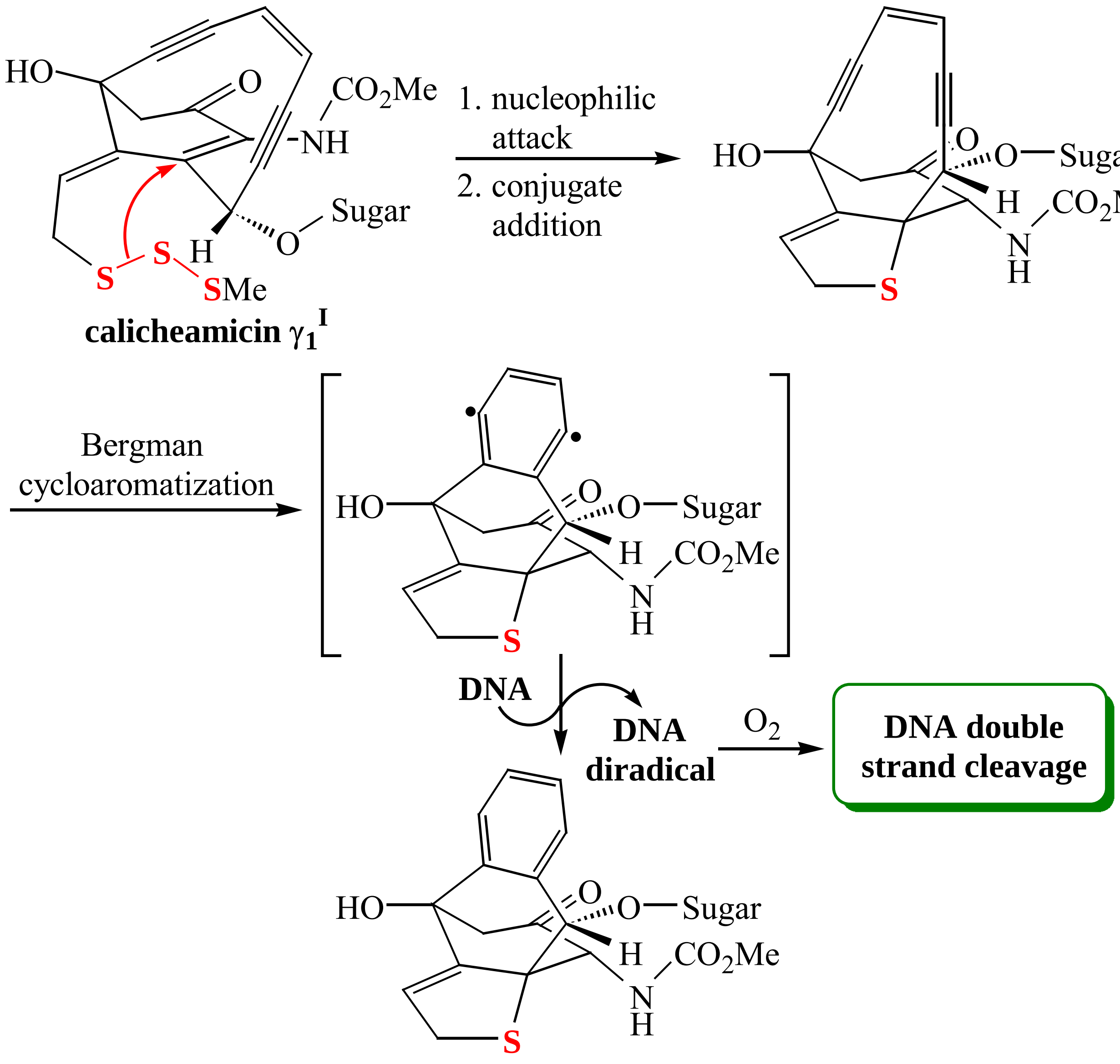


calicheamicin γ_1^I

3. The DNA-slicing property of calicheamicin γ_1^I arises because it acts as a molecular machine for producing carbon radicals.
   1) A carbon radical is a highly reactive and unstable intermediate that has an unpaired electron.
   2) A carbon radical can become a stable molecule again by removing a proton and one electron (i.e., a hydrogen atom) from another molecule.
   3) The molecule that lost the hydrogen atom becomes a new radical intermediate.

4) When the radical weaponry of each calicheamicin γ_1^{I} is activated, it removes a hydrogen atom from the backbone of DNA.

5) This leaves the DNA molecule as an unstable radical intermediate, which in turn results in double strand cleavage of the DNA and cell death.



4. The total synthesis of calicheamicin γ_1^{I} by the research group of K. C. Nicolaou (The Scripps Research Institute, University of California, San Diego) represents a stunning achievement in synthetic organic chemistry.

10.1 INTRODUCTION:

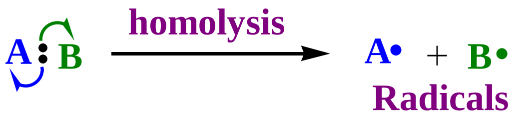
1. **Ionic reactions** are those in which covalent bonds break **heterolytically**, and in which ions are involved as reactants, intermediates, or products.

   1) **Heterolytic bond dissociation** (**heterolysis**): electronically ***unsymmetrical*** bond breaking ⇒ produces **ions**.

   2) **Heterogenic bond formation:** electronically ***unsymmetrical*** bond making.

   3) **Homolytic bond dissociation** (**homolysis**): electronically ***symmetrical*** bond breaking ⇒ produces **radicals** (**free radicals**).

   4) **Hemogenic bond formation:** electronically ***symmetrical*** bond making.

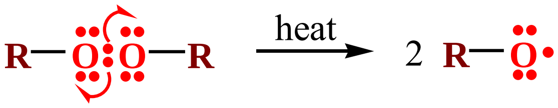


   i) **Single-barbed arrows** are used for the movement of **a single electron**.

10.1A PRODUCTION OF RADICALS

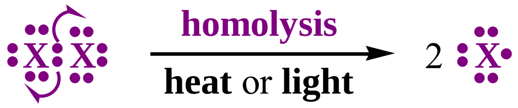
1. Energy must be supplied by **heating** or by **irradiation with light** to cause **homolysis** of covalent bonds.

   1) Homolysis of **peroxides:**



Dialkyl peroxide **Alkxoyl radicals**

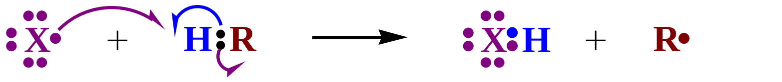
   2) Homolysis of **halogen molecules:** heating or irradiation with light of a wave length that can be absorbed by the halogen molecules.



10.1B REACTIONS OF RADICALS:

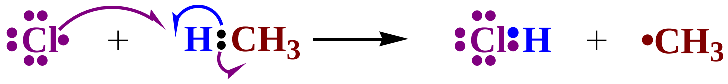
1. Almost all small radicals are short-lived, highly reactive species.
2. They tend to react in a way that leads to pairing of their unpaired electron.
   1) **Abstraction of an atom** from another molecule:
      i) **Hydrogen abstraction:**

General Reaction



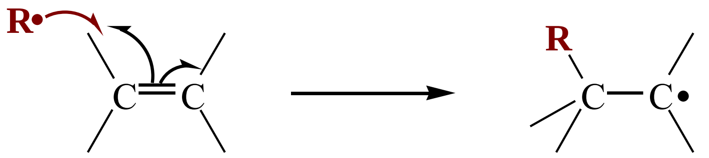
Alkane — Alkyl radical

Specific Example



Methane — Methyl radical

   2) **Addition** to a compound containing a **multiple bond** to produce a new, larger radical:



Alkene — New radical

The Chemistry of Radicals in Biology, Medicine, and Industry

1. Radical reactions are of vital importance in biology and medicine.
   1) Radical reactions are ubiquitous (everywhere) in living things, because radicals are produced in the normal course of metabolism.
   2) Radical are all around us because molecular oxygen ($\cdot\ddot{\underset{..}{O}}-\ddot{\underset{..}{O}}\cdot$) is itself a diradical.
   3) Nitric oxide ($\cdot\ddot{N}=\ddot{O}$:) plays a remarkable number of important roles in living systems.

i) Although in its free form nitric oxide is a relatively unstable and potentially toxic gas, in **biological system** it is involved in **blood pressure regulation** and **blood clotting**, **neurotransmission**, and the **immune response** against tumor cells.

ii) The 1998 Nobel Prize in Medicine was awarded to the scientists (R. F. Furchgott, L. J. Ignarro, and F. Murad) who discovered that NO is an important signaling molecule (chemical messenger).

2. Radical are capable of randomly damaging all components of the body because they are highly reactive.

1) Radical are believed to be important in the "**aging process**" in the sense that radicals are involved in the development of the chronic diseases that are life limiting.

2) Radical are important in the development of cancers and in the development of atherosclerosis (動脈粥樣硬化).

3. Superoxide ($\mathbf{O_2^{\bar{\bullet}}}$) is a naturally occurring radical and is associated with both the immune response against pathogens and at the same time the development of certain diseases.

1) An enzyme called superoxide dismutase regulates the level of superoxide in the body.

4. Radicals in cigarette smoke have been implicated in inactivation of an antiprotease in the lungs which leads to the development of emphysema (氣腫).

5. Radical reactions are important in many industrial processes.

1) Polymerization: polyethylene (PE), Teflon (polytetrafluoroethylene, PTFE), polystyrene (PS), and *etc*.

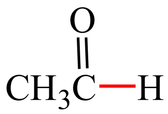
2) Radical reactions are central to the "cracking" process by which gasoline and other fuels are made from petroleum.

3) Combustion process involves radical reactions.

Table 10.1 Single-Bond Homolytic Dissociation Energies Δ*H*° at 25°C

$$A{:}B \longrightarrow A\bullet + B\bullet$$

Bond Broken (shown in red)	kJ mol^{-1}	Bond Broken (shown in red)	kJ mol^{-1}
H–H	435	$(CH_3)_2CH$–Br	285
D–D	444	$(CH_3)_2CH$–I	222
F–F	159	$(CH_3)_2CH$–OH	385
Cl–Cl	243	$(CH_3)_2CH$–OCH_3	337
Br–Br	192	$(CH_3)_2CHCH_2$–H	410
I–I	151	$(CH_3)_3C$–H	381
H–F	569	$(CH_3)_3C$–Cl	328
H–Cl	431	$(CH_3)_3C$–Br	264
H–Br	366	$(CH_3)_3C$–I	207
H–I	297	$(CH_3)_3C$–OH	379
CH_3–H	435	$(CH_3)_3C$–OCH_3	326
CH_3–F	452	$C_6H_5CH_2$–H	356
CH_3–Cl	349	CH_2=$CHCH_2$–H	356
CH_3–Br	293	CH_2=CH–H	452
CH_3–I	234	C_6H_5–H	460
CH_3–OH	383	HC≡C–H	523
CH_3–OCH_3	335	CH_3–CH_3	368
CH_3CH_2–H	410	CH_3CH_2–CH_3	356
CH_3CH_2–F	444	CH_3CH2CH_2–H	356
CH_3CH_2–Cl	341	CH_3CH_2–CH_2CH_3	343
CH_3CH_2–Br	289	$(CH_3)_2CH$–CH_3	351
CH_3CH_2–I	224	$(CH_3)_3C$–CH_3	335
CH_3CH_2–OH	383	HO–H	498
CH_3CH_2–OCH_3	335	HOO–H	377
$CH_3CH_2CH_2$–H	410	HO–OH	213
$CH_3CH_2CH_2$–F	444	$(CH_3)_3CO$–$OC(CH_3)_3$	157
$CH_3CH_2CH_2$–Cl	341	$C_6H_5C(=O)O$–$OC(=O)C_6H_5$	139
$CH_3CH_2CH_2$–Br	289		
$CH_3CH_2CH_2$–I	224		
$CH_3CH_2CH_2$–OH	383	CH_3CH_2O–OCH_3	184
$CH_3CH_2CH_2$–OCH_3	335	CH_3CH_2O–H	431
$(CH_3)_2CH$–H	395		
$(CH_3)_2CH$–F	439		364

$(CH_3)_2CH–Cl$ 339 

10.2 HOMOLYTIC BOND DISSOCIATION ENERGIES

1. **Bond formation is an exothermic process:**

H• + **H•** ⟶ **H–H** **Δ*H*° = – 435 kJ mol$^{–1}$**

Cl• + **Cl•** ⟶ **Cl–Cl** **Δ*H*° = – 243 kJ mol$^{–1}$**

2. **Bond breaking is an endothermic process:**

H–H ⟶ **H•** + **H•** **Δ*H*° = + 435 kJ mol$^{–1}$**

Cl–Cl ⟶ **Cl•** + **Cl•** **Δ*H*° = + 243 kJ mol$^{–1}$**

3. The **hemolytic bond dissociation energies**, **Δ*H*°**, of hydrogen and chlorine:

H–H	**Cl–Cl**
(Δ*H*° = 435 kJ mol$^{–1}$)	**(Δ*H*° = 243 kJ mol$^{–1}$)**

10.2A HOMOLYTIC BOND DISSOCIATION ENERGIES AND HEATS OF REACTION:

1. **Bond dissociation energies** can be used to calculate the enthylpy change (Δ*H*°) for a reaction.

1) For **bond breaking Δ*H*°** is **positive** and for **bond formation Δ*H*°** is **negative**.

H—H + **Cl—Cl** ⟶ 2 **H—Cl**

Δ*H*° = 435 kJ mol$^{–1}$ **Δ*H*° = 243 kJ mol$^{–1}$**
+678 kJ mol$^{–1}$ is required for bond cleavage.

(Δ*H*° = 431 kJ mol$^{–1}$) × 2
– 862 kJ mol$^{–1}$ is evolved in bond formation.

i) The overall reaction is exothermic:

$$\Delta H° = (– 862 \text{ kJ mol}^{–1} + 678 \text{ kJ mol}^{–1}) = – 184 \text{ kJ mol}^{–1}$$

ii) The following pathway is assumed in the calculation:

H–H ⟶ 2 **H•**

$$Cl\text{–}Cl \longrightarrow 2\ Cl\bullet$$

$$2\ H\bullet + 2\ Cl\bullet \longrightarrow 2\ H\text{–}Cl$$

10.2B Homolytic Bond Dissociation Energies and the Relative Stabilities of Radicals:

1. **Bond dissociation energies** can be used to eatimate the relative stabilities of radicals.
   1) $\Delta H°$ for 1° and 2° C–H bonds of propane:

      $CH_3CH_2CH_2\text{–}H$ ($\Delta H°$ = 410 kJ mol^{-1})

      $(CH_3)_2CH\text{–}H$ ($\Delta H°$ = 395 kJ mol^{-1})

   2) $\Delta H°$ for the reactions:

$$CH_3CH_2CH_2\text{–}H \longrightarrow CH_3CH_2CH_2\bullet + H\bullet \qquad \Delta H° = +410\ \text{kJ mol}^{-1}$$

Propyl radical
(a 1° radical)

$$(CH_3)_2CH\text{–}H \longrightarrow (CH_3)_2CH\bullet + H\bullet \qquad \Delta H° = +395\ \text{kJ mol}^{-1}$$

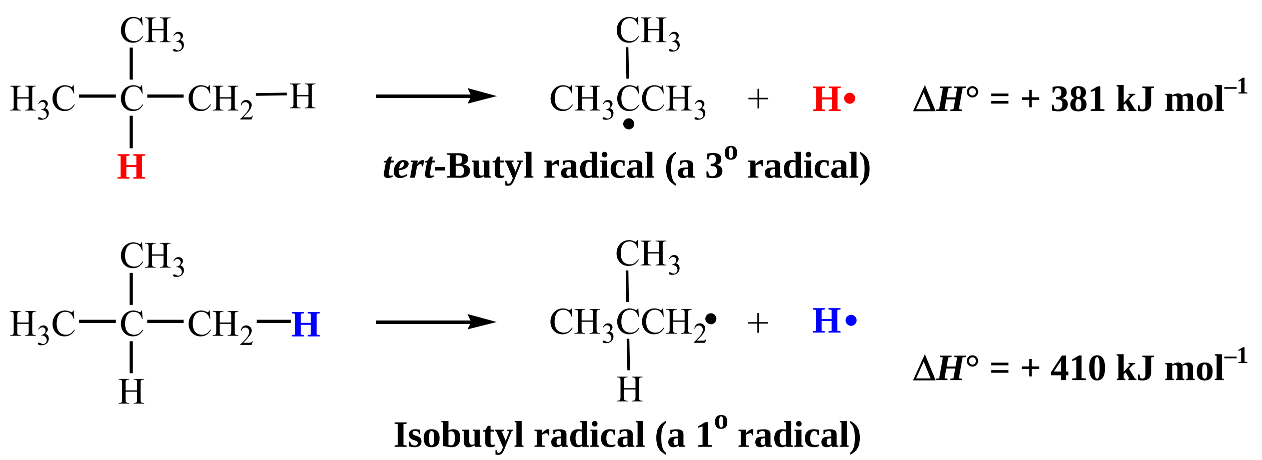
Isopropyl radical
(a 2° radical)

   3) These two reactions both begin with the same alkane (propane), and they both produce an alkyl radical and a hydrogen atom.
   4) They differ in the amount of energy required and in the type of carbon radical produced.

2. Alkyl radicals are classified as being 1°, 2°, or 3° on the basis of the carbon atom that has the unpaired electron.
   1) More energy must be supplied to produce a 1° alkyl radical (the propyl radical) from propane than is required to produce a 2° carbon radical (the isopropyl radical) from the same compound ⇒ **1° radical has greater potential energy** ⇒ **2° radical is the more stable radical**.

3. Comparison of the *tert*-butyl radical (a 3° radical) and the isobutyl radical (a 1° radical) relative to isobutene:

1) 3° radical is more than the 1° radical by 29 kJ mol^{-1}.



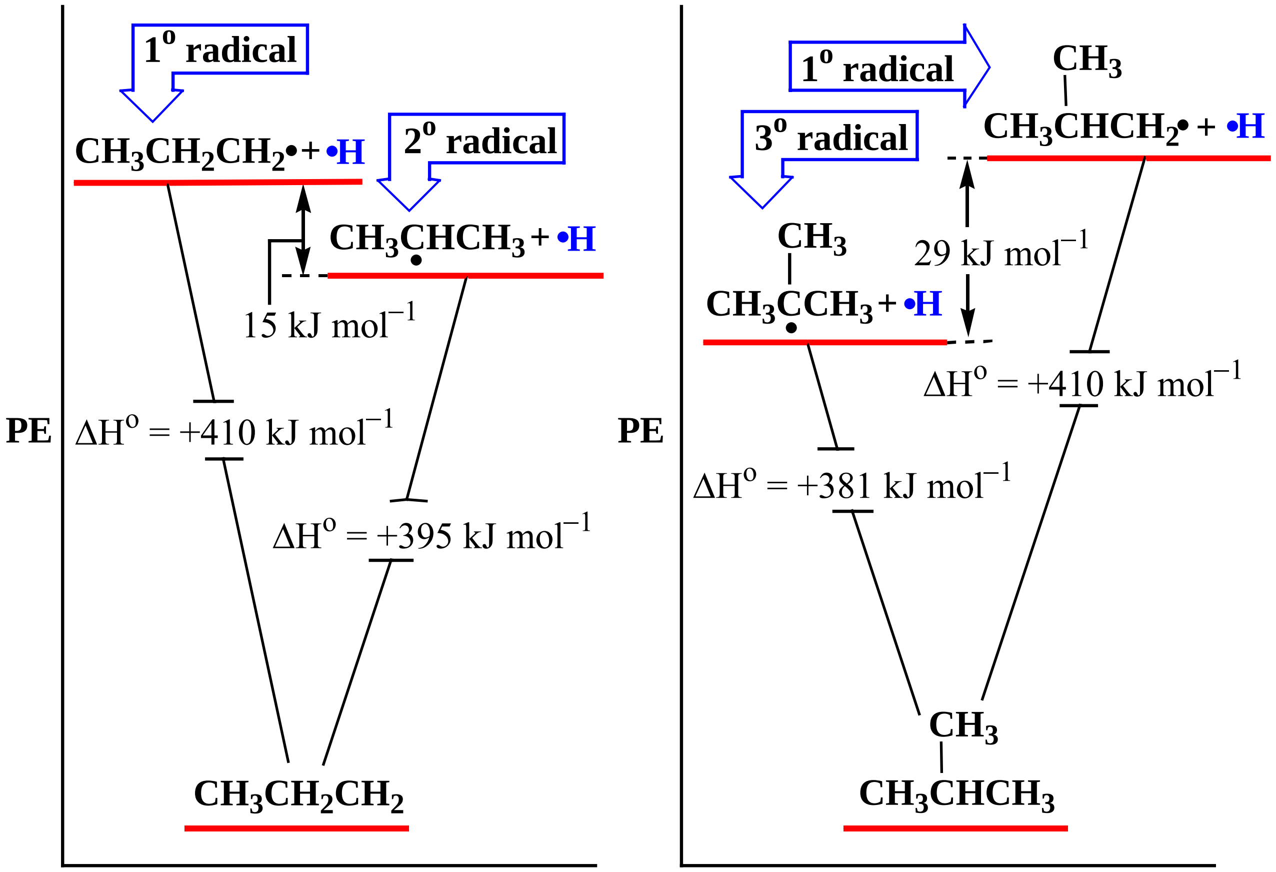
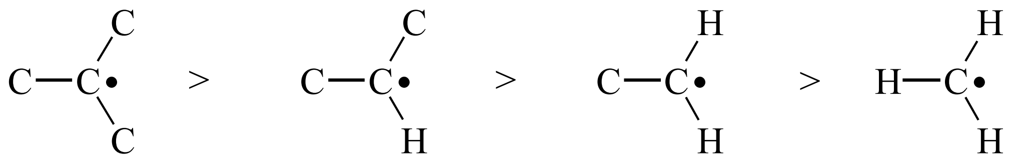


Figure 10.1 (a) Comparison of the potential energies of the propyl radical (+H•) and the isopropyl radical (+H•) relative to propane. The isopropyl radical — a 2° radical — is more stable than the 1° radical by 15 kJ $mole^{-1}$. (b) Comparison of the potential energies of the *tert*-butyl radical (+H•) and the isobutyl radical (+H•) relative to isobutane. The 3° radical is more stable than the 1° radical by 29 kJ $mole^{-1}$.

4. The relative stabilities of alkyl radicals:

Tertiary > Secondary > Primary > Methyl



1) The order of stability of alkyl radicals is the same as for carbocations.

i) Although alkyl radicals are uncharged, the carbon that bears the odd electrons is ***electron deficient***.

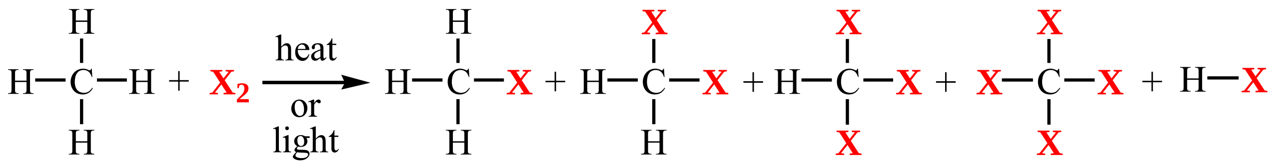
ii) Electron-releasing alkyl groups attached to this carbon provide a stabilizing effect, and more alkyl groups that are attached to this carbon, the more stable the radical is.

10.3 THE REACTIONS OF ALKANES WITH HALOGENS

1. Methane, ethane, and other alkanes react with fluorine, chlorine, and bromine.

1) Alkanes do not react appreciably with iodine.

2) With methane the reaction produces a mixture of halomethanes and a HX.



Methane Halogen Halo-methane Dihalo-methane Trihalo-methane Tetrahalo-methane Hydrogen halide

(*The sum of the number of moles of each halogenated methane produced equals the number of moles of methane that reacted.*)

2. **Halogentaiton** of an alkane is a **substitution reaction**.

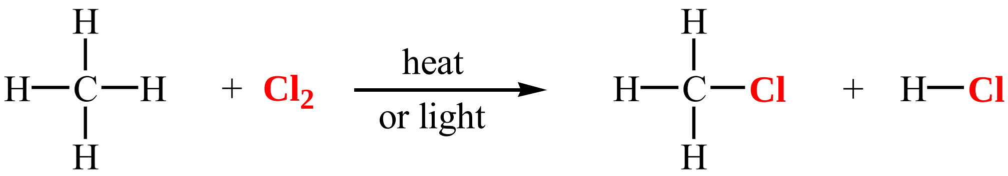
$$\textbf{R–H} + \textbf{X}_2 \longrightarrow \textbf{R–X} + \textbf{H–X}$$

10.3A MULTIPLE SUBSTITUTION REACTIONS VERSUS SELECTIVITY

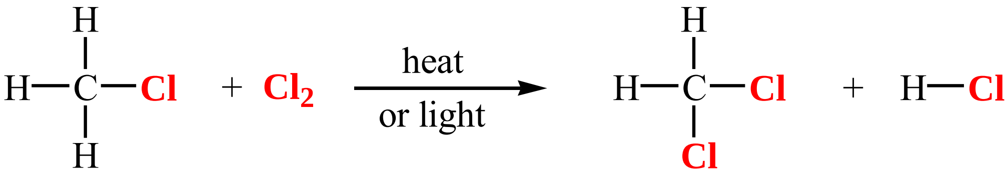
1. Multiple substitutions almost always occur in the halogenation of alkanes.

2. Chlorination of methane:

1) At the outset, the only compounds that are present in the mixture are chlorine and methane ⇒ the only reaction that can take place is the one that produces chloromethane and hydrogen chloride.



2) As the reaction progresses, the concentration of chloromethane in the mixture increases and a second substitution reaction begins to occur ⇒ Chloromethane reacts with chlorine to produce dichloromethane.

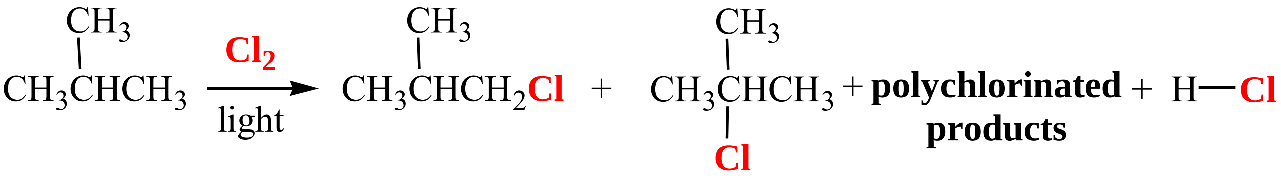


3) The dichloromethane produced can then react to form trichloromethane.

4) The trichloromethane, as it accumulates in the mixture, can react to produce tetrachloromethane.

3. Chlorination of most of higher alkanes gives a mixture of isomeric monochloro products as well as more highly halogenated compounds.

1) Chlorine is relatively ***unselective*** ⇒ it does not discriminate greatly among the different types of hydrogen atoms (1°, 2°, and 3°) in an alkane.

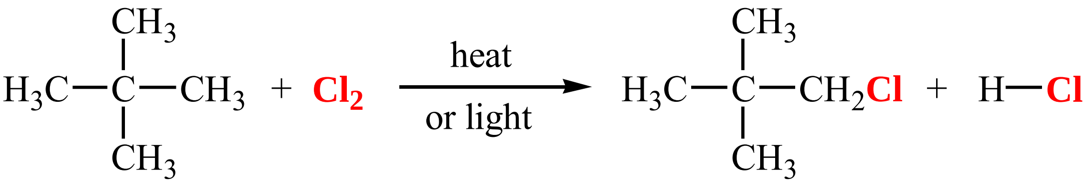


Isobutane **Isobutyl chloride (48%)** ***tert*-Buty chloride (29%)** **(23%)**

4. Alkane chlorinations usually give a complex mixture of products ⇒ they are not

generally useful synthetic methods for the preparation of a specific alkyl chloride.

1) Halogenation of an alkane (or cycloalkane) with equivalent hydrogens:



Neopentane (excess) **Neopentyl chloride**

5. Bromine is generally less reactive toward alkanes than chlorine ⇒ bromination is ***more regio-selective***.

10.4 CHLORINATION OF METHANE: MECHANISM OF REACTION

1. Several important experimental observations about halogenation reactions:

$$\mathbf{CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl} \quad (+\ \mathbf{CH_2Cl_2},\ \mathbf{CHCl_3},\ \text{and}\ \mathbf{CCl_4})$$

1) **The reaction is promoted by heat or light**.

i) At room temperature methane and chlorine do not react at a perceptible rate as long as the mixture is kept away from light.

ii) Methane and chlorine do react at room temperature if the gaseous reaction mixture is irradiated with UV light.

iii) Methane and chlorine do react in the dark if the gaseous reaction mixture is heated to temperatures greater than 100°C.

2) **The light-promoted reaction is highly efficient**.

10.4A A MECHANISM FOR THE HALOGENATION REACTION:

1. The ***chlorination*** (***halogenation***) reaction takes place by a **radical mechanism**.
2. The first step is the fragmentation of a chlorine molecule, by heat or light, into two chlorine atoms.

1) The frequency of light that promotes the chlorination of methane is a frequency that is absorbed by chlorine molecules and not by methane molecules.

A Mechanism for the Reaction

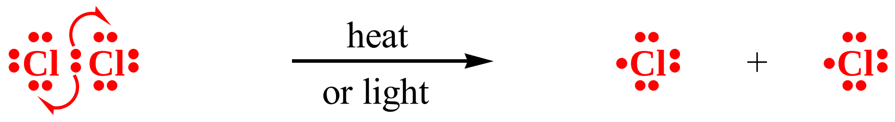
Radical Chlorination of Methane

Reaction:

$$CH_4 + Cl_2 \xrightarrow[\text{or light}]{\text{heat}} CH_3Cl + HCl$$

Mechanism:

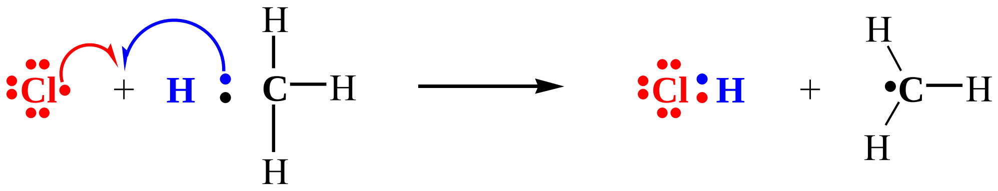
Step 1 (**chain-initiating step — radicals are created**)



Under the influence of heat or light a molecule of chlorine dissociates; each atom takes one of the bonding electrons.

This step produces two highly reactive chlorine atoms.

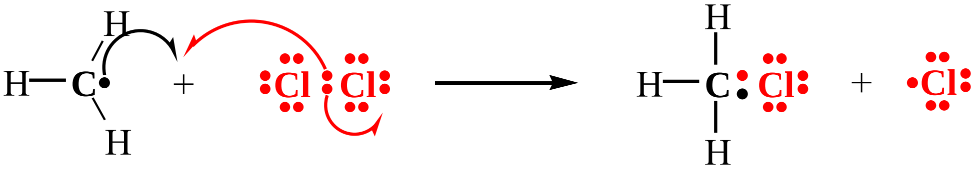
Step 2 (**chain-propagating step — one radical generates another**)



A chlorine atom abstracts a hydrogen atom from a methane molucule.

This step produces a molecule of hydrogen chloride and a methyl radical.

Step 3 (**chain-propagating step — one radical generates another**)



A methyl radical abstracts a chlorine atom from a chlorine molecule.

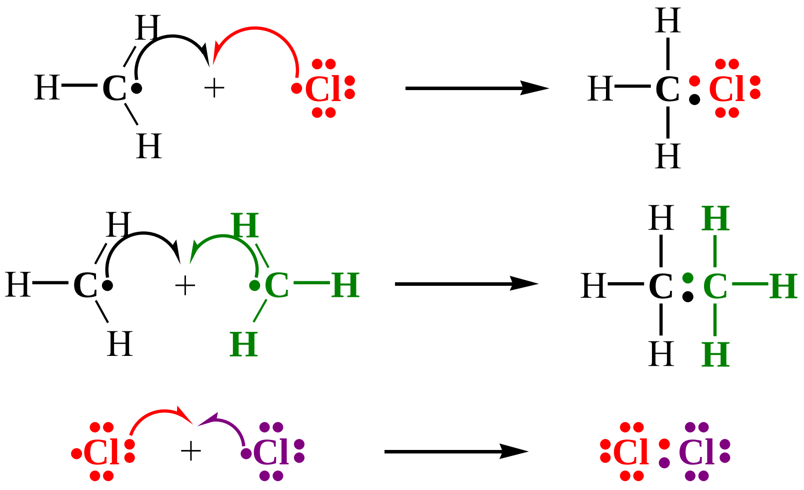
This step produces a molecule of methyl chloride and a cholrine atom. The chlorine atom can now cause a repetition of Step 2.

3. With repetition of steps 2 and 3, molecules of chloromethane and HCl are

procuded ⇒ **chain reaction**.

1) The chain reaction accounts for the observation that the light-promoted reaction is highly efficient.

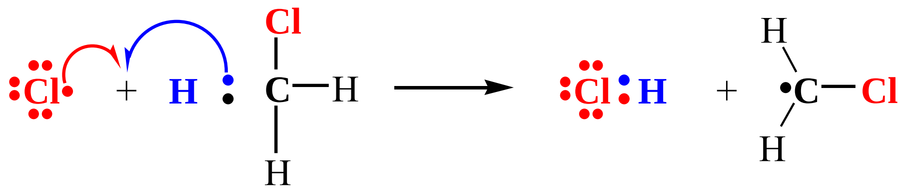
4. **Chain-terminating steps: used up one or both radical intermediates.**



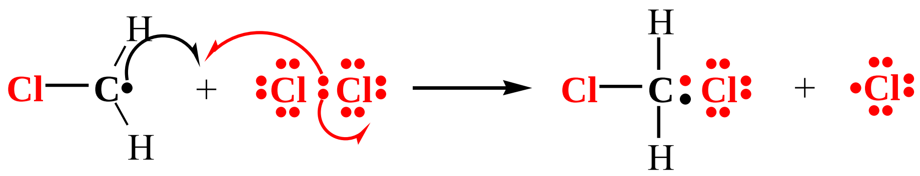
1) Chloromethan and ethane, formed in the terminating steps, can dissipate their excess energy through vibrations of their C–H bonds.
2) The simple diatomic chlorine that is formed must dissipate its excess energy rapidly by colliding with some other molecule or the walls of the container. Otherwise it simply flies apart again.

5. Mechanism for the formation of CH_2Cl_2:

***Step 2*a**



***Step 3*a**



10.5 CHLORINATION OF METHANE: ENERGY CHANGES

1. **The heat of reaction for each individual step of the chlorination:**

Chain Initiation

Step 1	Cl–Cl (Δ*H*° = 243) ⟶ 2 Cl•		Δ*H*° = + 243 kJ mol^{-1}

$$\text{Cl–Cl}\ (\Delta H^\circ = 243) \longrightarrow 2\ \text{Cl}\bullet \qquad \Delta H^\circ = +243\ \text{kJ mol}^{-1}$$

Chain Propagation

Step 2

$$CH_3\text{–H}\ (\Delta H^\circ = 435) + \bullet\text{Cl} \longrightarrow CH_3\bullet + \text{H–Cl}\ (\Delta H^\circ = 431) \qquad \Delta H^\circ = +4\ \text{kJ mol}^{-1}$$

Step 3

$$CH_3\bullet + \text{Cl–Cl}\ (\Delta H^\circ = 243) \longrightarrow CH_3\text{–Cl}\ (\Delta H^\circ = 349) + \bullet\text{Cl} \qquad \Delta H^\circ = -106\ \text{kJ mol}^{-1}$$

Chain Termination

$$CH_3\bullet + \bullet\text{Cl} \longrightarrow CH_3\text{–Cl}\ (\Delta H^\circ = 349) \qquad \Delta H^\circ = -349\ \text{kJ mol}^{-1}$$

$$CH_3\bullet + CH_3\bullet \longrightarrow CH_3\text{–}CH_3\ (\Delta H^\circ = 368) \qquad \Delta H^\circ = -368\ \text{kJ mol}^{-1}$$

$$\bullet\text{Cl} + \bullet\text{Cl} \longrightarrow \text{Cl–Cl}\ (\Delta H^\circ = 243) \qquad \Delta H^\circ = -243\ \text{kJ mol}^{-1}$$

2. In the **chain-initiating step** only the bond between two chlorine atoms is broken, and no bonds are formed.
   1) The heat of reaction is simply the bond dissociation energy for a chlorine molecule, and it is highly endothermic.

3. In the **chain-terminating steps** bonds are formed, but no bonds are borken.
   1) All of the chain-terminating steps are highly exothermic.

4. In the **chain-propagating steps**, requires the breaking of one bond and the formation of another.
   1) The value of Δ*H*° for each of these steps is the difference between the bond dissociation energy of the bond that is broken and the bond dissociation energy for the bond that is formed.

5. The addition of **chain-propagating steps** yields the overall equation for the chlorination of methane:

$$CH_3–H + •Cl \longrightarrow CH_3• + H–Cl \qquad \Delta H° = +4 \text{ kJ mol}^{-1}$$
$$CH_3• + Cl–Cl \longrightarrow CH_3–Cl + •Cl \qquad \Delta H° = -106 \text{ kJ mol}^{-1}$$

$$CH_3–H + Cl–Cl \longrightarrow CH_3–Cl + H–Cl \qquad \Delta H° = -102 \text{ kJ mol}^{-1}$$

1) The addition of the values of $\Delta H°$ for the **chain-propagating steps** yields the overall value of $\Delta H°$ for the reaction.

10.5A THE OVERALL FREE-ENERGY CHANGE:

1. For many reactions the entropy change is so small that the term $T\Delta S°$ is almost zero, and $\Delta G°$ is approximately equal to $\Delta H°$ in $\Delta G° = \Delta H° - T\Delta S°$.
2. Degrees of freedom are associated with ways in which ***monement or changes in relative position can occur*** for a molecule and its constituent atoms.

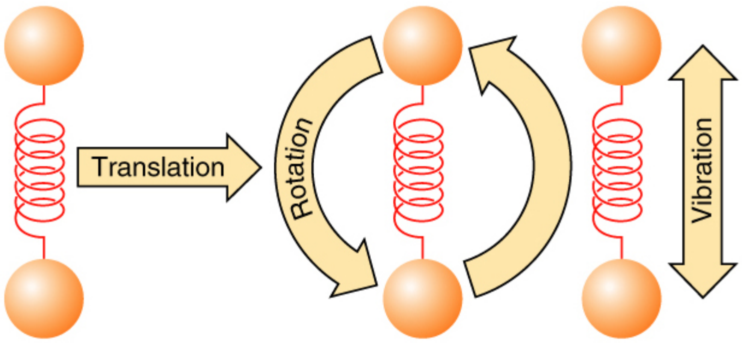


Figure 10.2 Translational, rotational, and vibrational degrees of freedom for a simple diatomic molecule.

3. The reaction of methane with chlorine:

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$$

1) 2 moles of the products are formed from 2 moles of the reactants ⇒ the number of **translational degrees of freedom** available to products and reactants are the same.

2) CH_3Cl is a tetrahedral molecule like CH_4, and HCl us a diatomic molecule like Cl_2 ⇒ the number of **vibrational** and **rotational degrees of freedom** available to products and reactants are approximately the same.

3) The entropy change for this reaction is quite small, $\Delta S° = +2.8 \text{ J K}^{-1} \text{ mol}^{-1}$ ⇒ at

room temperature (298 K) the $T\Delta S°$ term is 0.8 kJ mol^{-1}.

4) The enthalpy change for the reaction and the free-energy change are almost equal ⇒ $\Delta H° = -102.5$ kJ mol^{-1} and $\Delta G° = -103.3$ kJ mol^{-1}.

5) In situation like this one it is often convenient to make predictions about whether a reaction will proceed to completion on the basis of $\Delta H°$ rather than $\Delta G°$ since $\Delta H°$ values are readily obtained from bond dissociation energies.

10.5B ACTIVATION ENERGIES:

1. It is often convenient to estimate the reaction rates simply on **energies of activation**, E_{act}, rather than on **free energies of activation**, $\Delta G^{\ddagger}$.
2. E_{act} and $\Delta G^{\ddagger}$ are close related and **both measure the difference in energy between the reactants and the transition state**.
   1) A low **energy of activation** ⇒ a reaction will take place rapidly.
   2) A high **energy of activation** ⇒ a reaction will take place slowly.

3. The **energy of activation** for each step in chlorination:

Chain Initiation

Step 1 $Cl_2 \longrightarrow 2\ Cl\bullet$ $\qquad$ $E_{act} = +243$ kJ mol^{-1}

Chain Propagation

Step 2 $CH_3\text{–}H + \bullet Cl \longrightarrow CH_3\bullet + H\text{–}Cl$ $\qquad$ $E_{act} = +16$ kJ mol^{-1}

Step 3 $CH_3\bullet + Cl\text{–}Cl \longrightarrow CH_3\text{–}Cl + \bullet Cl$ $\qquad$ $E_{act} = \sim 8$ kJ mol^{-1}

   1) The **energy of activation** must be determined from other experimental data.
   2) The **energy of activation** cannot be directly measured — it is calculated.

4. Principles for estimating **energy of activation**:
   1) **Any reaction in which *bonds* are broken will have an energy of activation greater than zero.**
      i) **This will be true even if a stronger bond is formed and the reaction is exothermic.**
      ii) **Bond formation and bond breaking do not occur simultaneously in the**

transition state.

iii) **Bond formation lags behind, and its energy is not all available for bond breaking.**

2) **Activation energies of endothermic reactions that involve both bond formation and bond rupture will be greater than the heat of reaction, Δ*H*°.**

$$CH_3\text{–}H + \bullet Cl \longrightarrow CH_3\bullet + H\text{–}Cl \qquad \Delta H° = +4\ \text{kJ mol}^{-1}$$
$$(\Delta H° = 435) \qquad (\Delta H° = 431) \qquad E_{act} = +16\ \text{kJ mol}^{-1}$$

$$CH_3\text{–}H + \bullet Br \longrightarrow CH_3\bullet + H\text{–}Br \qquad \Delta H° = +69\ \text{kJ mol}^{-1}$$
$$(\Delta H° = 435) \qquad (\Delta H° = 366) \qquad E_{act} = +78\ \text{kJ mol}^{-1}$$

i) This energy released in bond formation is less than that required for bond breaking for the above two reactions ⇒ they are **endothermic** reactions.

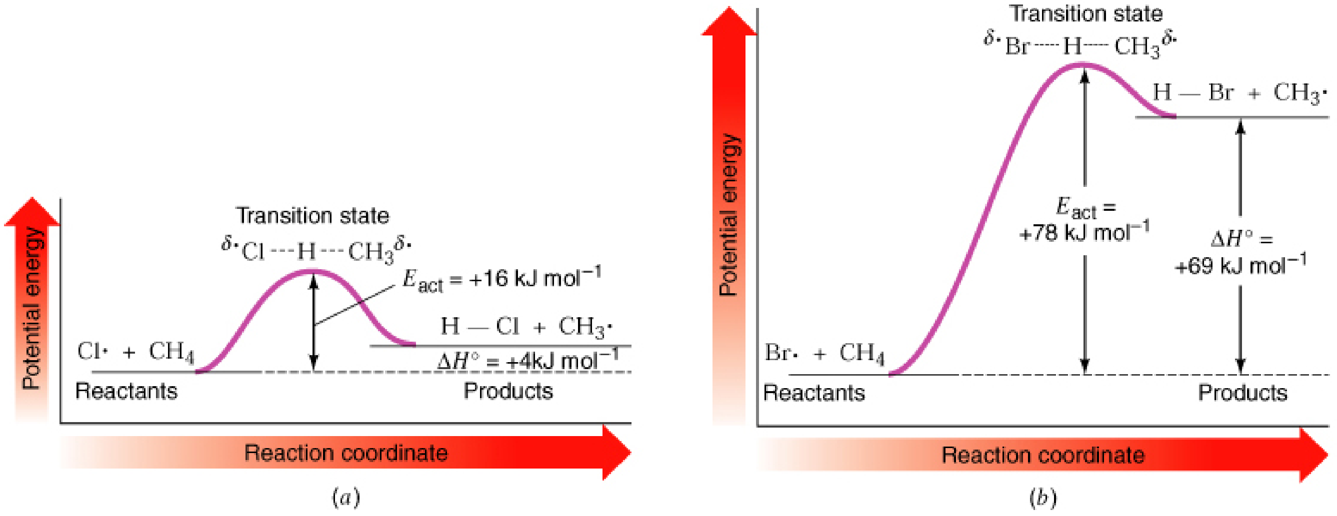


Figure 10.3 **Potential energy diagrams (a) for the reaction of a chlorine atom with methane and (b) for the reaction of a bromine atom with methane.**

3) **The energy of activation of a gas-phase reaction where bonds are broken homolytically but no bonds are formed is equal to Δ*H*°.**

i) This rule only applies to radical reactions taking place in the gas phase.

$$Cl\text{–}Cl \longrightarrow 2\ \bullet Cl \qquad \Delta H° = +243\ \text{kJ mol}^{-1}$$
$$(\Delta H° = 243) \qquad E_{act} = +243\ \text{kJ mol}^{-1}$$

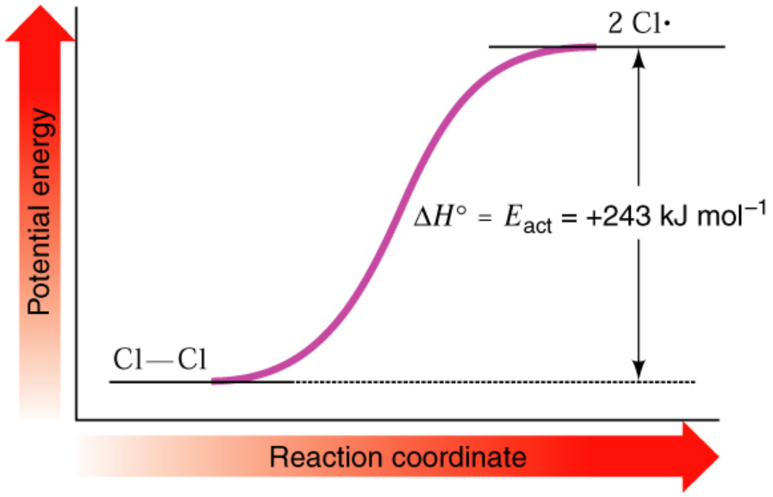


Figure 10.4 **Potential energy diagram for the dissociation of a chlorine molecule into chlorine atoms.**

4) **The energy of activation for a gas-phase reaction in which radicals combine to form molecules is usually zero.**

$$2\ CH_3\bullet \longrightarrow CH_3{-}CH_3 \qquad \Delta H^\circ = -368\ kJ\ mol^{-1}$$

$$(\Delta H^\circ = 368) \qquad E_{act} = 0\ kJ\ mol^{-1}$$

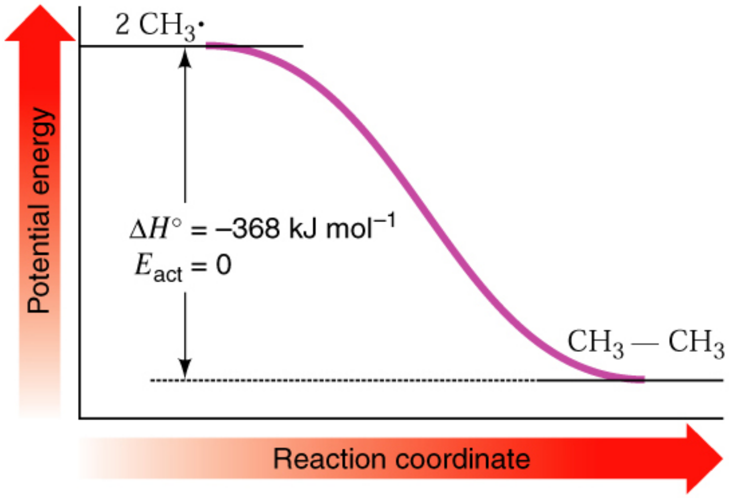


Figure 10.5 **Potential energy diagram for the combination of two methyl radicals to form a molecule of ethane.**

10.5C REACTION OF METHANE WITH OTHER HALOGENS:

1. The ***reactivity*** of one substance toward another is measured by the ***rate*** at which the two substances react.

1) Fluorine is most reactive — so reactive that without special precautions mixtures

of fluorine and methane explode.

2) Chlorine is the next most reactive — chlorination of methane is easily controlled by the judicious control of heat and light.

3) Bromine is much less reactive toward methane than chlorine.

4) Iodine is so unreactive that the reaction between it and methane does not take place for all practical purposes.

2. The ***reactivity*** of halogens can be explained by their $\Delta H°$ and E_{act} for each step:

1) **FLUORINATION:**

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$F_2 \longrightarrow 2\,F\bullet$	+ 159	+ 159
Chain Propagation		
$F\bullet + CH_3\text{–}H \longrightarrow H\text{–}F + CH_3\bullet$	– 134	+ 5.0
$CH_3\bullet + F\text{–}F \longrightarrow CH_3\text{–}F + F\bullet$	– 293	Small
Overall $\Delta H°$ =	**– 427**	

i) The chain-initiating step in fluorination is highly endothermic and thus has a high energy of activation.

ii) One initiating step is able to produce thousands of fluorination reactions ⇒ the high activation energy for this step is not an obstacle to the reaction.

iii) Chain-propagating steps cannot afford to have high energies of activation.

iv) Both of the chain-propagating steps in fluorination have very small energies of activation.

v) The overall heat of reaction, $\Delta H°$, is very large ⇒ large quantity of heat is evolved as the reaction occurs ⇒ the heat may accumulate in the mixture faster than it dissipates to the surroundings ⇒ causing the reaction temperature to rise ⇒ a rapid increase in the frequency of additional chain-initiating steps that would generate additional chains.

vi) The low energy of activation for the chain-propagating steps and the large

overall heat of reaction ⇒ high reactivity of fluorine toward methane..

vii) Fluorination reactions can be controlled by diluting both the hydrocarbon and the fluorine with an inert gas such as helium or the reaction can be carried out in a reactor packed with copper shot to absorb the heat produced.

2) CHLORINATION:

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$Cl_2 \longrightarrow 2\ Cl\bullet$	+ 243	+ 243
Chain Propagation		
$Cl\bullet + CH_3{-}H \longrightarrow H{-}Cl + CH_3\bullet$	+ 4	+ 16
$CH_3\bullet + Cl{-}Cl \longrightarrow CH_3{-}Cl + Cl\bullet$	– 106	Small
Overall $\Delta H°$ =	**– 102**	

i) The higher energy of activation of the first chain-propagating step in chlorination (16 kJ mol^{-1}), versus the lower energy of activation (5.0 kJ mol^{-1}) in fluorination, partly explains the lower reactivity of chlorine.

ii) The greater energy required to break the Cl–Cl bond in the initiating step (243 kJ mol^{-1} for Cl_2 versus 159 kJ mol^{-1} for F_2) has some effect, too.

iii) The much greater overall heat of reaction in fluorination probably plays the greatest role in accounting for the much greater reactivity of fluorine.

3) BROMINATION:

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$Br_2 \longrightarrow 2\ Br\bullet$	+ 192	+ 192
Chain Propagation		
$Br\bullet + CH_3{-}H \longrightarrow H{-}Br + CH_3\bullet$	+ 69	+ 78
$CH_3\bullet + Br{-}Br \longrightarrow CH_3{-}Br + Br\bullet$	– 100	Small

Overall $\Delta H°$ = – 31

i) The chain-initiating step in bromination has a very high energy of activation (E_{act} = 78 kJ mol^{-1}) ⇒ only a very tiny fraction of all of the collisions between bromine and methane molecules will be energetically effective even at a temperature of 300 °C.

ii) Bromine is much less reactive toward methane than chlorine even though the net reaction is slightly exothermic.

4) **IODINATION:**

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$I_2 \longrightarrow 2\,I•$	+ 151	+ 151
Chain Propagation		
$I• + CH_3–H \longrightarrow H–I + CH_3•$	+ 138	+ 140
$CH_3• + I–I \longrightarrow CH_3–I + I•$	– 84	Small

Overall $\Delta H°$ = + 54

i) The I–I bond is weaker than the F–F bond ⇒ the chain-initiating step is not responsible for the observed reactivities: $F_2 > Cl_2 > Br_2 > I_2$.

ii) The H-abstraction step (the first chain-propagating step) determines the order of reactivity.

iii) The energy of activation for the first chain-propagating step in iodination reaction (140 kJ mol^{-1}) is so large that only two collisions out of every 10^{12} have sufficient energy to produce reactions at 300 °C.

5) The halogenation reactions are quite similar and thus have similar entropy changes ⇒ the relative reactivities of the halogens toward methane can be compared on energies only.

10.6 HALOGENATION OF HIGHER ALKANES

1. Ethane reacts with chlorine to produce chloroethane:

A Mechanism for the Reaction

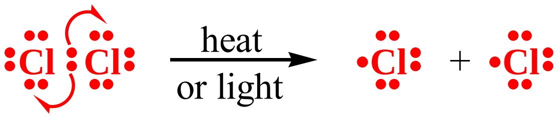
Radical Chlorination of Ethane

Reaction:

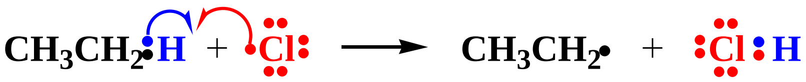
$$CH_3CH_3 + Cl_2 \xrightarrow[\text{or light}]{\text{heat}} CH_3CH_2Cl + HCl$$

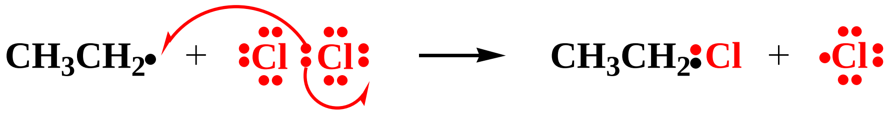
Mechanism:

Chain Initiation



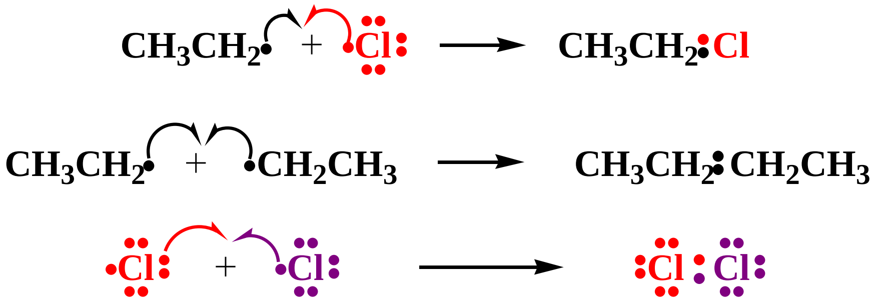
Chain Propagation

Step 2 

Step 3 

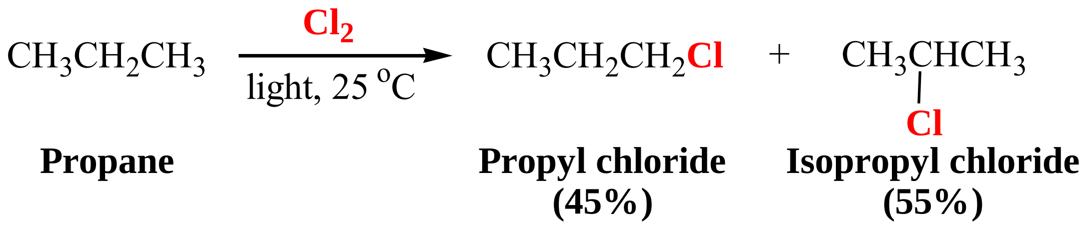
Chain propagation continues with Step 2, 3, 2, 3, an so on.

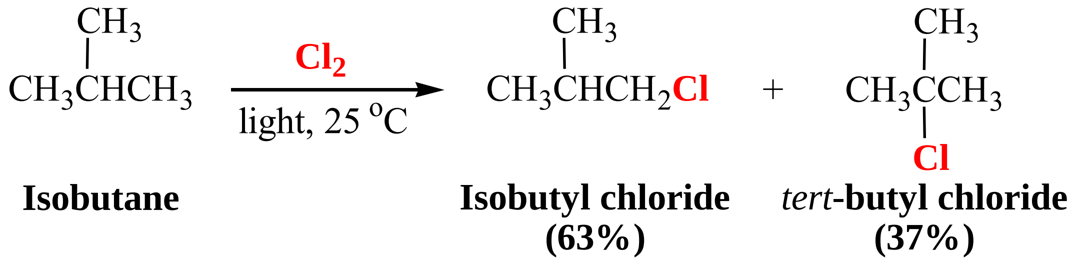
Chain Termination

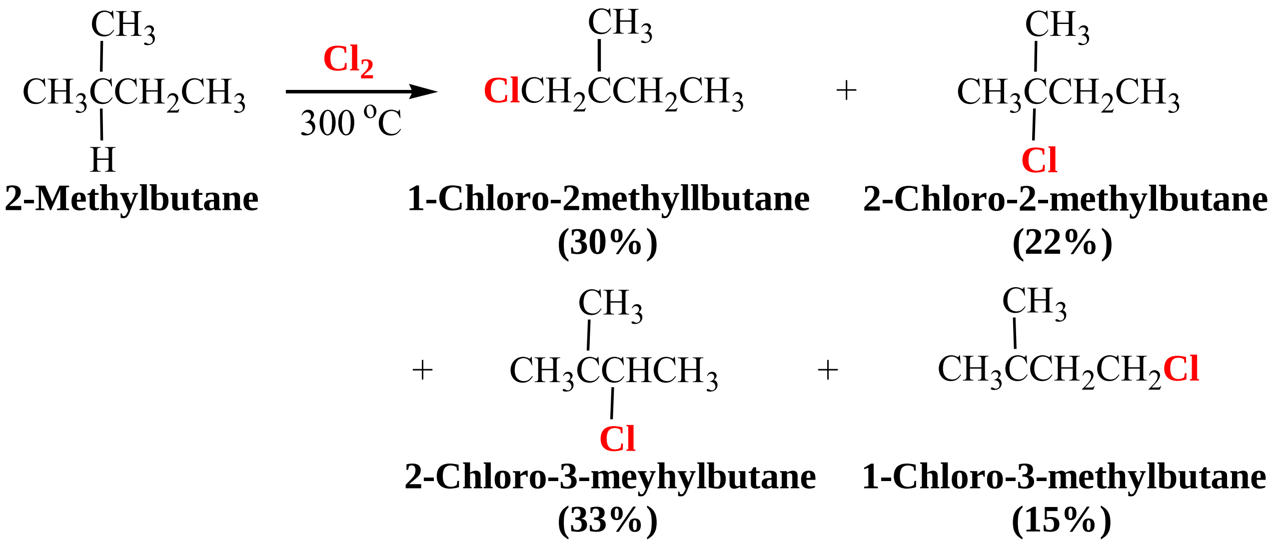


2. Chlorination of most alkanes whose molecules contain more than two carbon atoms gives a mixture of isomeric monochloro products (as well as more highly chlorinated compounds).

1) The percentages given are based on the total amount of monochloro products formed in each reaction.







2) **3° hydrogen atoms of an alkane are most reactive**, **2° hydrogen atoms are next most reactive**, and **1° hydrogen atoms are the least reactive**.

3) Breaking a **3° C–H bond requires the least energy**, and breaking a **1° C–H bond requires the most energy**.

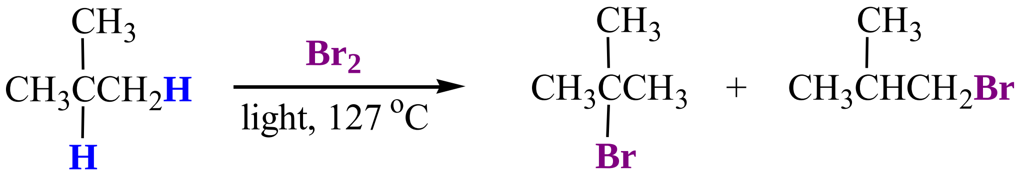
4) The step in which the C–H bond is broken determines the location or orientation of the chlorination ⇒ the E_{act} for abstracting a 3° hydrogen atom to be the least and the E_{act} for abstracting a 1° hydrogen atom to be greatest ⇒ **3° hydrogen atoms should be most reactive**, **2° hydrogen atoms should be the next most reactive**, and **1° hydrogen atoms should be the the least reactive**.

5) The difference in the rates with which 1°, 2°, and 3° hydrogen atoms are

replaced by chlorine are not large ⇒ chlorine does not discriminate among the different types of hydrogen atoms to render chlorination of higher alknaes a generally useful laboratory synthesis.

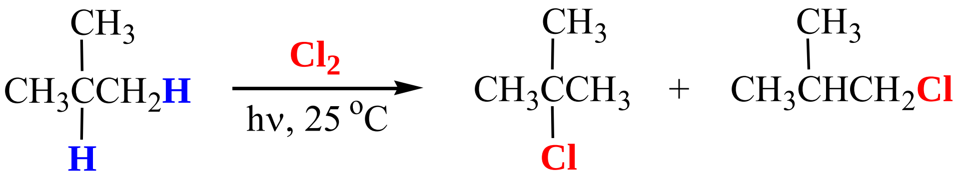
10.6A SELECTIVITY OF BROMINE

1. Bromine is less reactive toward alkanes in general than chlorine, but bromine is more ***selective*** in the site of attack when it does react.
2. The reaction of isobutene and bromine gives almost exclusive replacement of the 3° hydrogen atom.



(>99%) **(trace)**

i) The ratio for chlorination of isobutene:

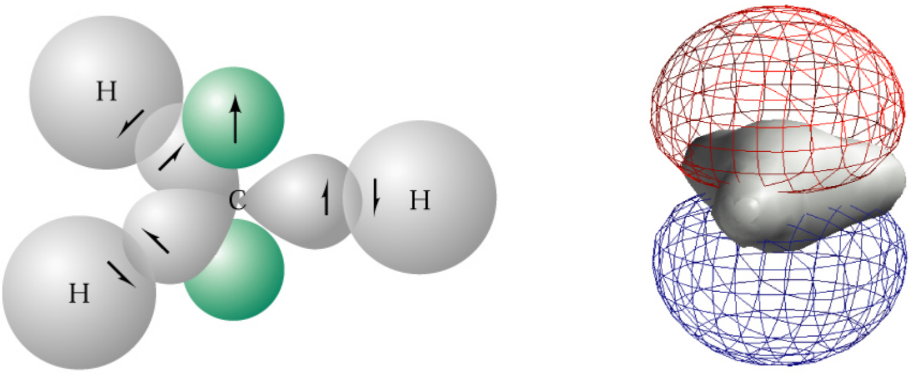


(37%) **(63%)**

3. Fluorine is much more reactive than chlorine ⇒ ***fluorine is even less selective than chlorine***.

10.7 THE GEOMETRY OF ALKYL RADICALS

1. The geometrical structure of most alkyl radicals is ***trigonal planar*** at the carbon having the unpaired electron.
   1) In an alkyl radical, the *p* orbital contains the unpaired electron.



(a) (b)

Figure 10.6 **(a) Drawing of a methyl radical showing the *sp*^{2}-hybridized carbon atom at the center, the unpaired electron in the half-filled *p* orbital, and the three pairs of electrons involved in covalent bonding. The unpaired electron could be shown in either lobe. (b) Calculated structure for the methyl radical showing the highest occupied molecular orbital, where the unpaired electron resides, in red and blue. The region of bonding electron density around the carbons and hydrogens is in gray.**

10.8 REACTIONS THAT GENERATE TETRAHEDRAL STEREOCENTERS

1. When achiral molecules react to produce a compound with a single tetrahedral stereocenter, the product will be obtained as a racemic form.

   1) The radical chlorination of pentane:

$$CH_3CH_2CH_2CH_2CH_3 \xrightarrow[\text{(achiral)}]{Cl_2} CH_3CH_2CH_2CH_2CH_2Cl + CH_3CH_2CH_2\overset{*}{C}HClCH_3$$

Pentane (achiral) — **1-Chloropentane (achiral)** — **(±)-2-Chloropentane (a racemic form)**

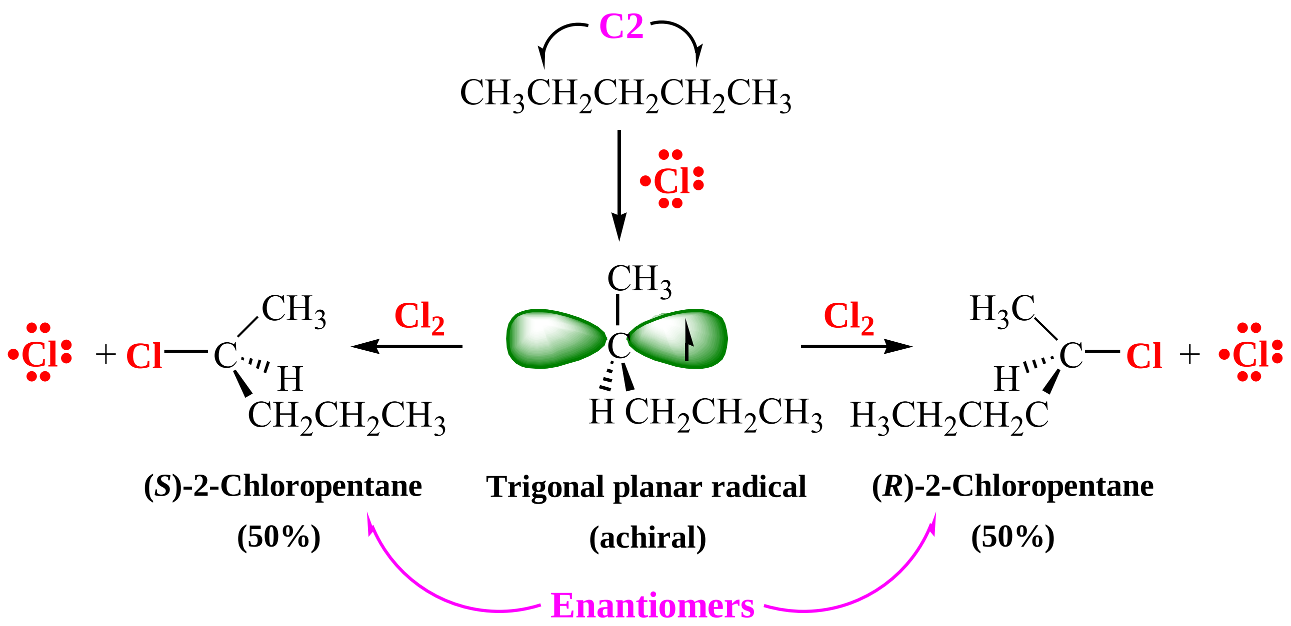
$$+ \quad CH_3CH_2CHClCH_2CH_3$$

3-Chloropentane (achiral)

   1) Neither 1-chloropentane nor 3-chloropentane contains a stereocenter, but 2-chloropentane does, and it is ***obtained as a racemic form***.

A Mechanism for the Reaction

The Stereochemistry of Chlorination at C2 of Pentane



Abstraction of a hydrogen atom from C2 produces a trigonal planar radical that is achiral. This radical is achiral then reacts with chlorine at either face [by path (a) or path (b)]. Because the radical is achiral the probability of reaction by either path is the same; therefore, the two enantiomers are produced in equal amounts, and a racemic form of 2-chloropentane results.

10.8A GENERATION OF A SECOND STEREOCENTER IN A RADICAL HALOGENATION:

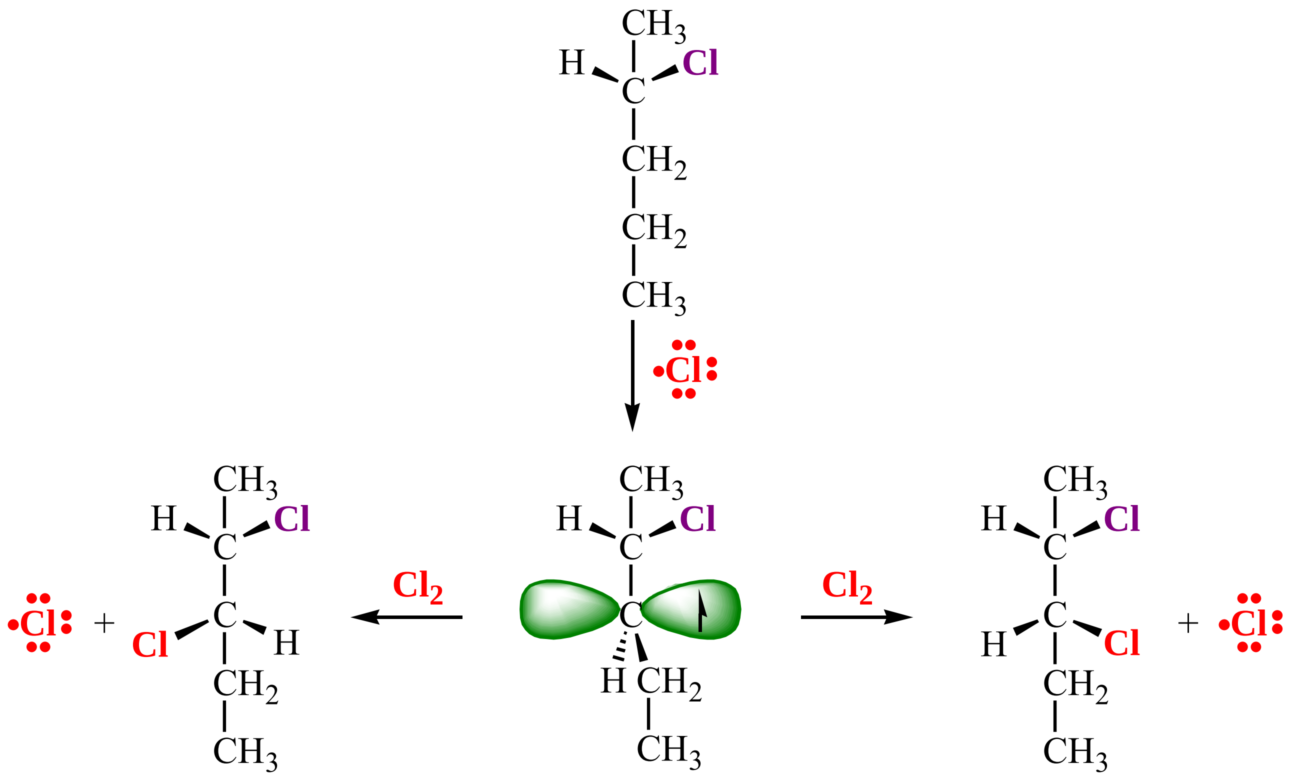
1. When a chiral molecule reacts to yield a product with a second stereocenter:
   1) The products of the reactions are **diastereomeric** (2*S*,3*S*)-2,3-dichloropentane and (2*S*,3*R*)-2,3-dichloropentane.
      i) The two diastereomers are ***not*** produced in equal amounts.
      ii) The intermediate radical itself is chiral ⇒ reactions at the two faces are not equally likely.
      iii) The presence of a stereocenter in the radical (at C2) influences the reaction that introduces the new stereocenter (at C3).

2) Both of the 2,3-dichloropentane diastereomers are ***chiral*** ⇒ each exhibits optical activity.

   i) The two diastereomers have ***different physical properties*** (e.g., m.p. & b.p.) and are separable by conventional means (by GC, LC, or by careful fractional distillation).

A Mechanism for the Reaction

The Stereochemistry of Chlorination at C3 of (*S*)-2-Chloropentane



(2*S*,3*S*)-2,3-Dichloropentane (chiral) | **Trigonal planar radical (chiral)** | **(2*S*,3*R*)-2,3-Dichloropentane (chiral)**

Abstraction of a hydrogen atom from C3 of (*S*)-2-chloropentane produces a radical that is chiral (it contains a stereocenter at C2). This chiral radical can then react with chlorine at one face [path (a)] to produce (2*S*,3*S*)-2,3-dichloropentane and at the other face [path (b)] to yield (2*S*,3*R*)-2,3-dichloropentane. These two compounds are diastereomers, and they are not produced in equal amounts. Each product is chiral, and each alone would be optically active.

10.9 REDICAL ADDITION TO ALKENES: THE ANTI-MARKOVNIKOV ADDITION OF HYDROGEN BROMIDE

1. Kharasch and Mayo (of the University of Chicago) found that when alkenes that contained peroxides or hydroperoxides reacted with HBr ⇒ anti-Markovnikov addition of HBr occurred.

R—Ö—Ö—R	R—Ö—Ö—H
An organic peroxide	**An organic hydroperoxide**

   1) In the presence of peroxides, propene yields 1-bromopropane.

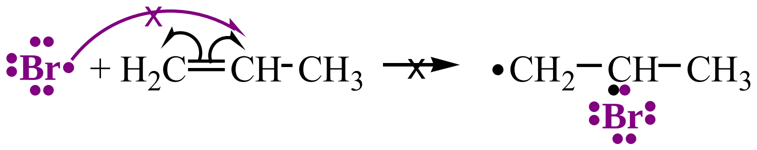
$$CH_3CH{=}CH_2 + \mathbf{HBr} \xrightarrow{ROOR} CH_3CH_2CH_2Br \quad \text{Anti-Markovnikov addition}$$

   2) In the absence of peroxides, or in the presence of compounds that would "trap" radicals, normal Markovnikov addition occurs.

$$CH_3CH{=}CH_2 + \mathbf{HBr} \xrightarrow[\text{peroxides}]{\text{no}} CH_3CHBrCH_2{-}\mathbf{H} \quad \text{Markovnikov addition}$$

2. **HF**, **HCl**, and **HI** ***do not*** give anti-Markovnikov addition even in the presence of peroxides.

3. Step 3 determines the final orientation of Br in the product because ***a more stable 2° radical*** is produced and because ***attack at the 1° carbon is less hindered***.

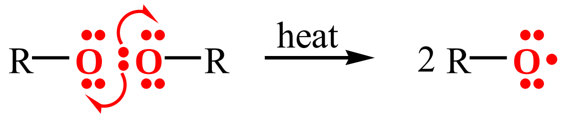


   1) Attack at the 2° carbon atom would have been more hindered.

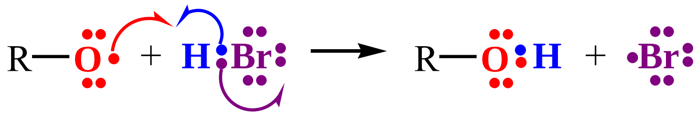
A Mechanism for the Reaction

Anti-Markovnikov Addition

Chain Initiation

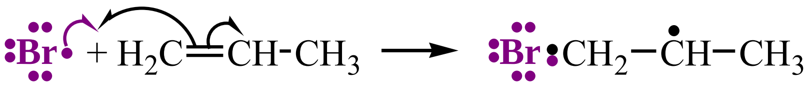
Step 1  $\Delta H° \cong +150$ kJ mol^{-1}

Heat brings about homolytic cleavage of the weak oxygen-oxygen bond.

Step 2  $\Delta H° \cong -96$ kJ mol^{-1}

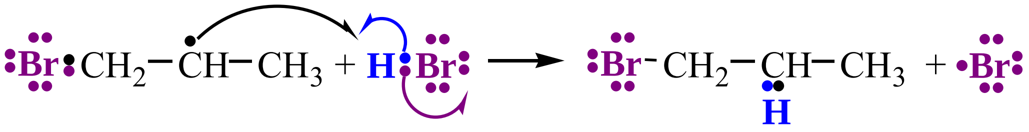
E_{act} is low

The alkoxyl radical abstracts a H-atom from HBr, producing a Br-atom.

Step 3 

2° radical

A Br-atom adds to the double bond to produce the more stable 2° radical.

Step 4 

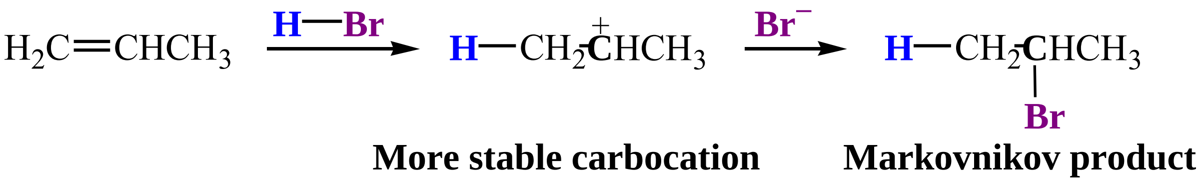
1-Bromopropane

The 2° radical abstracts a H-atom from HBr. This leads to the product and regenerates a Br-atom. Then repetitions of steps 3 and 4 lead to a chain reaction.

10.9A SUMMARY OF MARKOVNIKOV VERSUS ANTI-MARKOVNIKOV ADDITION OF HBr TO ALKENES

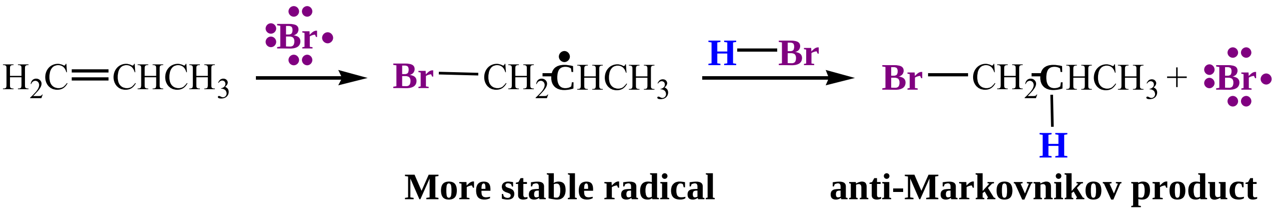
1. In the absence of peroxides, the reagent that attacks the double bond first is a proton.
   1) Proton is small ⇒ steric effects are unimportant.
   2) Proton attaches itself to a carbon atom by an ionic mechanism to form the more stable carbocation ⇒ Markovnikov addition.

Ionic addition



2. In the presence of peroxides, the reagent that attacks the double bond first is the larger bromine atom.
   1) Bromine attaches itself to the less hindered carbon atom by a radical mechanism to form the more stable radical intermediate ⇒ anti-Markovnikov addition.

Radical addition



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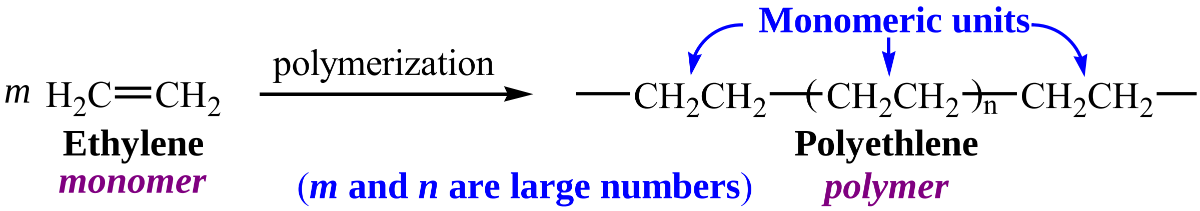
10.10 RADICAL POLYMERIZATION OF ALKENES: CHAIN-GROWTH POLYMERS

1. **Polymers**, called **macromolecules**, are made up of many repeating subunits (**monomers**) by **polymerization** reactions.
   1) Polyethylene (PE):



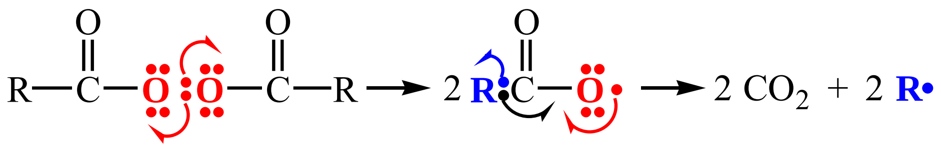
2. **Chain-growth polymers** (**addition polymers**):
   1) Ethylene polymerizes by a radical mechanism when it is heated at a pressure of 1000 atm with a small amount of an organic peroxide.
   2) The polyethylene is useful only when it has a molecular weight of nearly 1,000,000.
   3) Very high molecular weight polyethylene can be obtained by using a low concentration of the initiator ⇒ initiates the polymerization of only a few chains and ensures that each will have a large excess of the monomer available.

A Mechanism for the Reaction

Radical Polymerization of Ethene

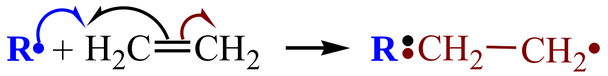
Chain Initiation

Step 1



Diacyl peroxide

Step 2



The diacyl peroxide dissociates to produce radicals, which in turn initiate chains.

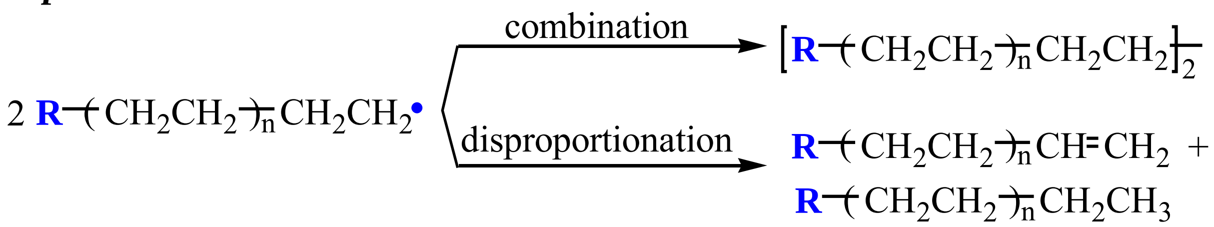
Chain Propagation

Step 3 $R{:}CH_2{-}CH_2\bullet + n\,H_2C{=}CH_2 \longrightarrow R{\leftarrow}CH_2CH_2{\rightarrow}_n CH_2CH_2\bullet$

Chain propagation by adding successive ethylene units, until their growth is stopped by combination or disproportionation.

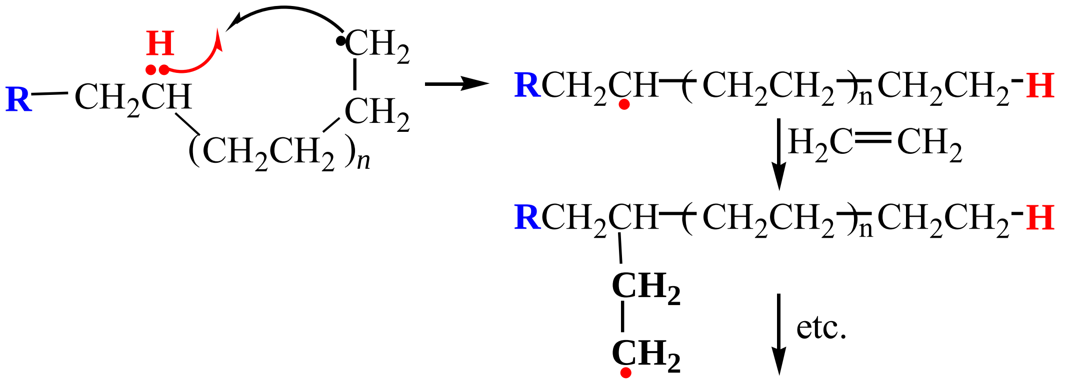
Chain Termination

Step 4



The radical at the end of the growing polymer chain can also abstract a hydrogen atom from itself by what is called "back biting." This leads to chain branching.

Chain Branching



3. Polyethylene has been produced commercially since 1943.

1) PE is used in manufacturing flexible bottles, films, sheets, and insulation for electric wires.

2) PE produced by radical polymerization has a softening point of about 110°C.

4. PE can be produced using **Ziegler-Natta catalysts** (organometallic complexes of transition metals) in which no radicals are produced, no back biting occurs, and, consequently, there is no chain branching.

1) The PE is of higher density, has a higher melting point, and has greater strength.

Table 10.2 Other Common Chain-Growth Polymers

Monomer	Polymer	Names
$CH_2{=}CHCH_3$	$-\!\!(CH_2-CH(CH_3))_n\!\!-$	Polypropylene
$CH_2{=}CHCl$	$-\!\!(CH_2-CH(Cl))_n\!\!-$	Poly(vinyl chloride), PVC
$CH_2{=}CHCN$	$-\!\!(CH_2-CH(CN))_n\!\!-$	Polyacrylonitrile, Orlon
$CF_2{=}CF_2$	$-\!\!(CF_2-CF_2)_n\!\!-$	Polytetrafluoroethene, Teflon
$H_2C{=}C(CH_3)CO_2CH_3$	$-\!\!(CH_2-C(CH_3)(CO_2CH_3))_n\!\!-$	Poly(methyl methacrylate), Lucite, Plexiglas, Perspex

10.11 Other Important Radical Chain Reactions

10.11A Molecular Oxygen and Superoxide

1. Molecular oxygen in the ground state is a diradical with one unpaired electron on

each oxygen.

1) As a radical, oxygen can abstract hydrogen atoms just like other radicals.

2. In biological systems, oxygen is an electron acceptor.

1) Molecular oxygen accepts one electron and becomes a radical anion called superoxide ($O_2^{\bullet -}$).

2) Superoxide is involved in both positive and negative physiological roles:

i) The immune system uses superoxide in its defense against pathogens.

ii) Superoxide is suspected of being involved in degenerative disease processes associated with aging and oxidative damage to healthy cells.

3) The enzyme superoxide dismutase regulates the level of superoxide by catalyzing conversion of superoxide to hydrogen peroxide and molecular oxygen.

i) Hydrogen peroxide is also harmful because it can produce hydroxyl (HO•) radicals.

ii) The enzyme catalase helps to prevent release of hydroxyl radicals by converting hydrogen peroxide to water and oxygen.

$$2\,O_2^{\bullet -} + 2\,H^+ \xrightarrow{\text{superoxide dismutase}} H_2O_2 + O_2$$

$$2\,H_2O_2 \xrightarrow{\text{catalase}} 2\,H_2O + O_2$$

10.11B COMBUSTION OF ALKANES

1. When alkanes react with oxygen a complex series of reactions takes place, ultimately converting the alkane to CO_2 and H_2O.

$$R\text{—}H + O_2 \longrightarrow R\bullet + \bullet OOH \quad \textbf{Initiating}$$

$$R\bullet + O_2 \longrightarrow R\text{—}OO\bullet$$

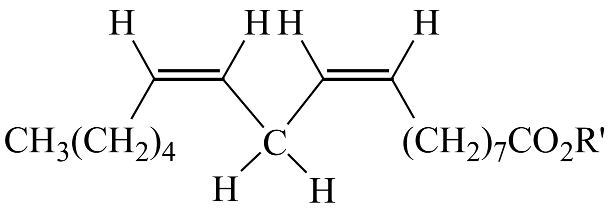
$$R\text{—}OO\bullet + R\text{—}H \longrightarrow R\text{—}OOH + R\bullet \quad \Big\} \textbf{Propagating}$$

2. The O–O bond of an alkyl hydroperoxide is quite weak, and it can break and produce radicals that can initiate other chains:

$$\text{RO–OH} \longrightarrow \text{RO}\bullet + \bullet\text{OH}$$

10.11C AUTOXIDATION

1. Linoleic acid is a ***polyunsaturated fatty acid*** (compound containing two or more double bonds) occurs as an ester in **polyunsaturated fats**.



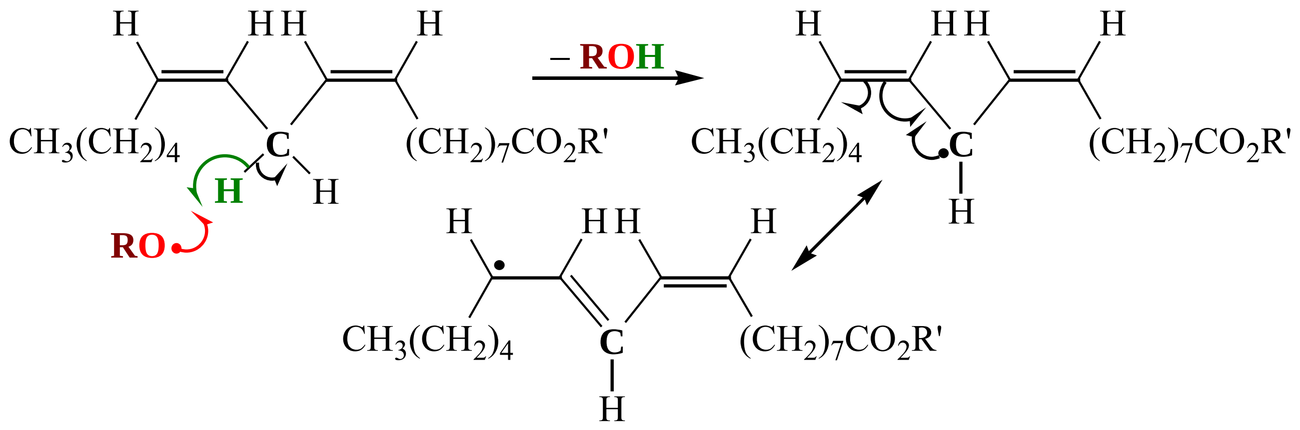
Linoleic acid (**as an ester**)

2. Polyunsaturated fats occur widely in the fats and oils that are components of our diet and are widespread in the tissues of the body where they perform numerous vital functions.

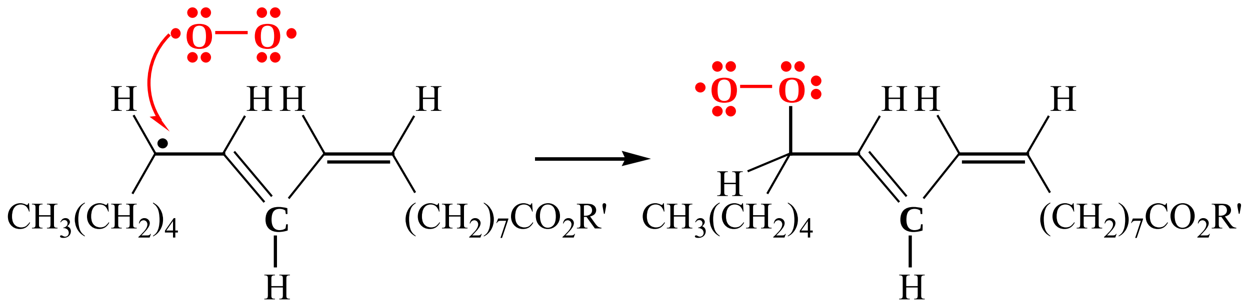
3. The hydrogen atoms of the $–CH_2–$ group located between the two double bonds of linoleic ester (**Lin–H**) are especially susceptible to abstraction by radicals.
   1) Abstraction of one of these hydrogen atoms produces a new radical (**Lin•**) that can react with oxygen in **autoxidation**.
   2) The result of **autoxidation** is the formation of a hydroperoxide.

4. **Autoxidation** is a process that occurs in many substances:
   1) **Autoxidation** is responsible for the development of the rancidity that occurs when fats and oils spoil and for the spontaneous combustion of oily rags left open to the air.
   2) **Autoxidation** occurs in the body which may cause irreversible damage.

Step 1 ***Chain initiation***



Step 2 ***Chain Propagation***



Step 3 ***Chain Propagation***

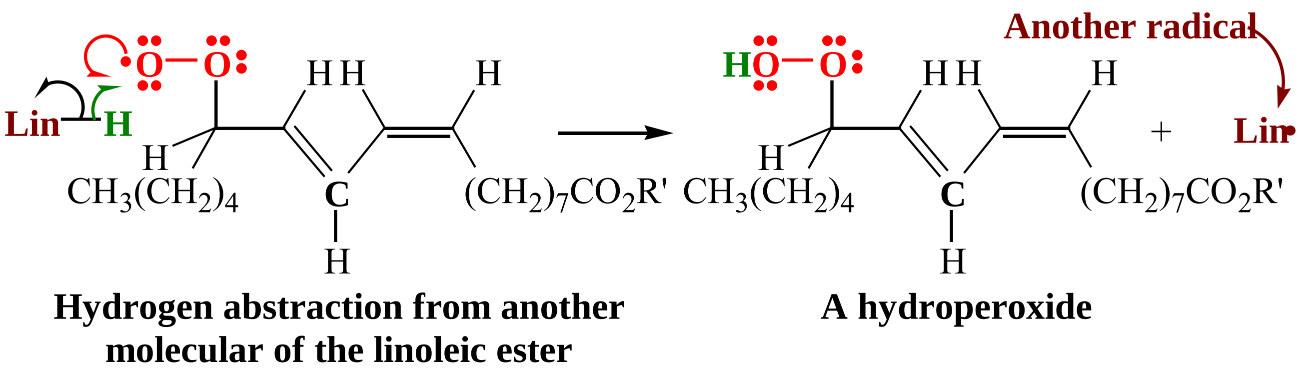


Figure 10.7 **Autoxidation of a linoleic acid ester. In step 1 the reaction is initiated by the attack of a radical on one of the hydrogen atoms of the –CH_2– group between the two double bonds; this hydrogen abstraction produces a radical that is a resonance hybrid. In step 2 this radical reacts with oxygen in the first of two chain-propagating steps to produce an oxygen-containing radical, which in step 3 can abstract a hydrogen from another molecule of the linoleic ester (Lin–H). The result of this second chain-propagating step is the formation of a hydroperoxide and a radical (Lin•) that can bring about a repetition of step 2.**

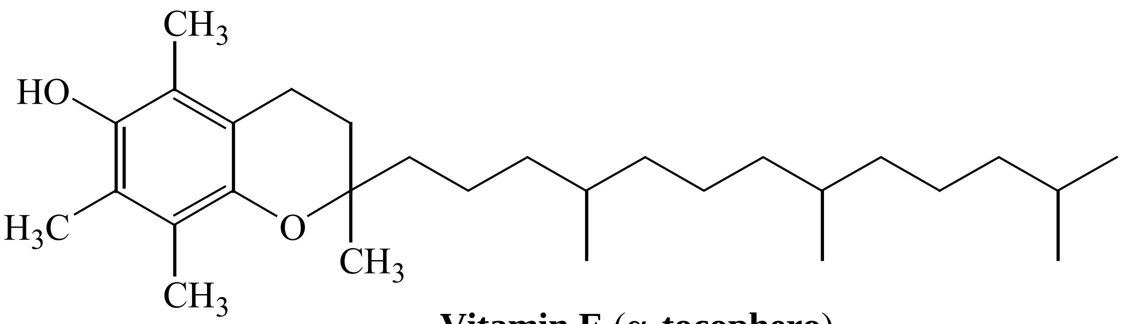
10.11D ANTIOXIDANTS

1. Autoxidation is inhibited by **antioxidants**.
   1) Antioxidants can rapidly "trap" peroxyl radicals by reacting with them to give stabilized radicals that do not continue the chain.

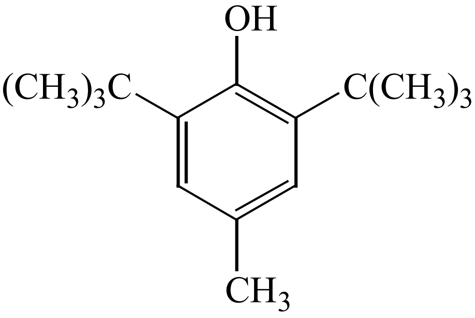
2. Vitamin E (α-tocopherol) is capable of acting as a radical trap which may inhibit radical reactions that could cause cell damage.

3. Vitamin C is also an antioxidant (supplements over 500 mg per day may have prooxidant effect).

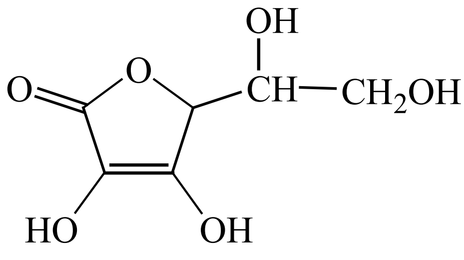
4. BHT is added to foods to prevent autoxidation.



Vitamin E (α-tocophero)



BHT
(butylated hydroxytoluene)



Vitamin C

10.11E OZONE DEPLETION AND CHLOROFLUOROCARBONS (CFCs):

1. In the stratosphere at altitudes of about 25 km, very high energy UV light converts diatomic oxygen (O_2) into ozone (O_3).

Step 1 $O_2 + h\nu \longrightarrow O + O$

Step 2 $O + O_2 + M \longrightarrow O_3 + M + heat$

Step 3 $O_3 + h\nu \longrightarrow O_2 + O + heat$

1) M is some other particle that can absorb some of the energy released in step 2.
2) The ozone produced in step 2 can also interact with high energy UV light give molecular oxygen and an oxygen atom in step 3.
3) The oxygen atom formed in step 3 can cause a repetition of step 2, and so forth.
4) The net result of these steps is to convert highly energetic UV light into heat.

2. Production of ***freons*** or chlorofluorocarbons (CFCs) (chlorofluoromethane and chlorofluoroethanes) began in 1930 and the world production reached 2 billion pounds annually by 1974.
   1) Freons have been used as refrigerants, solvents, and propellants in aerosol cans.
   2) Typical freons are trichlorofluoromethane, $CFCl_3$ (called Freon-11) and dichlorodifluoromethane, CF_2Cl_2 (called Freon-12).
   3) In the stratosphere freon is able to initiate radical chain reactions that can upset the natural ozone balance (1995 Nobel Prize in Chemistry was awarded to P. J. Crutzen, M. J. Molina, and F. S. Rowland).
   4) The reactions of Freon-12:

Chain Initiation

Step 1 $CF_2CCl_2 + h\nu \longrightarrow CF_2CCl\bullet + Cl\bullet$

Chain Propagation

Step 2 $Cl\bullet + O_3 \longrightarrow ClO\bullet + O_2$

Step 3 $ClO\bullet + O \longrightarrow O_2 + Cl\bullet$

3. In 1985 a hole was discovered in the ozone layer above Antarctica.
   1) The "Montreal Protocol" was initiated in 1987 which required the reduction of production and consumption of chlorofluorocarbons.

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ALCOHOLS AND ETHERS

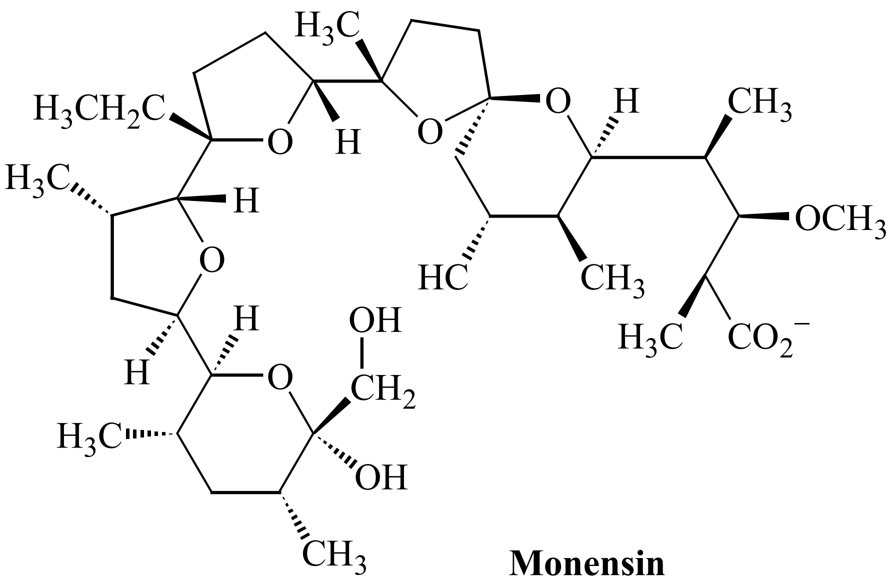
MOLECULAR HOSTS

1. The cell membrane establishes critical **concentration gradients** between the interior and exterior of cells.
   1) An intracellular to extracellular difference in sodium and potassium ion concentrations is essential to the function of nerves, transport of important nutrients into the cell, and maintenance of proper cell volume.
      i) Discovery and characterization of the actual molecular pump that establishes the sodium and potassium concentration gradient (Na^+, K^+-ATPase) earned Jens Skou (Aarhus University, Denmark) one half of the 1997 Nobel Prize in Chemistry. The other half went to Paul D. Boyer (UCLA) and John E. Walker (Cambridge) for elucidating the enzymatic mechanism of ATP synthesis.

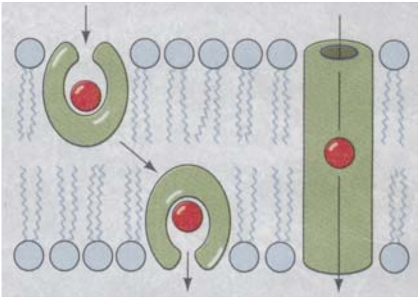
2. There is a family of antibiotics (**ionophores**) whose effectiveness results from disrupting this crucial ion gradient.

3. Monesin binds with sodium ions and carries them across the cell membrane and is called a ***carrier*** **ionophore**.
   1) Other ionophore antibiotics such as gramicidin and valinomycin are ***channel-forming*** **ionophores** because they open pores that extend through the membrane.
   2) The ion-transporting ability of monensin results principally from its many ether functional groups, and it is an example of a polyether antibiotic.
      i) The oxygen atoms of these molecules bind with metal ions by Lewis acid-base interactions.
      ii) Each monensin molecule forms an octahedral complex with a sodium ion.
      iii) The complex is a hydrophobic "host" for the ion that allows it to be carried as a "guest" of monensin from one side of the nonpolar cell membrane to the other.
      iv) The transport process destroys the critical sodium concentration gradient

needed for cell function.



Monensin



Carrier (left) and channel-forming modes of transport ionophors.

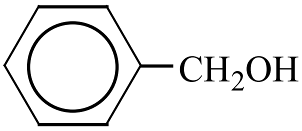
4. Crown ethers are molecular "hosts" that are also polyether ionophores.
   1) Crown ethers are useful for conducting reactions with ionic reagents in nonpolar solvents.
   2) The 1987 Nobel Prize in Chemistry was awarded to Charles J. Pedersen, Donald J. Cram, and Jean-Marie Lehn for their work on crown ethers and related compounds (host-guest chemisty).

11.1 STRUCTURE AND NOMENCALTURE

1. **Alcohols** are compounds whose molecules have a hydroxyl group attached to a ***saturated*** carbon atom.

1) Compounds in which a hydroxyl group is attached to an ***unsaturated*** carbon atom of a double bond (i.e., C=C–OH) are called **enols**.

CH_3OH	CH_3CH_2OH	$CH_3CH(OH)CH_3$	$CH_3C(CH_3)(OH)CH_3$
Methanol **(methyl alcohol)**	**Ethanol** **(ethyl alcohol)** ***a 1° alcohol***	**2-Propanol** **(isopropyl alcohol)** ***a 2° alcohol***	**2-Methyl-2propanol** **(*tert*-butyl alcohol)** ***a 3° alcohol***



Benzyl alcohol
a benzylic alcohol

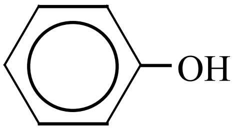
CH_2=$CHCH_2OH$

2-Propenol
(allyl alcohol)
an allylic alcohol

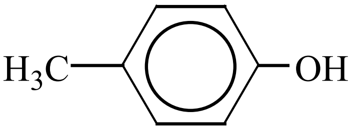
H–C≡CCH_2OH

2-Propynol
(propargyl alcohol)

2) Compounds that have a hydroxyl group attached directly to a ***benzene ring*** are called **phenols**.



Phenol



***p*-Methylphenol (*p*-Cresol)**

Ar–OH

General formula

2. **Ethers** are compounds whose molecules have an oxygen atom bonded to **two** carbon atom.

1) The hydrocarbon groups may be alkyl, alkenyl, vinyl, alkynyl, or aryl.

CH_3CH_2–O–CH_2CH_3

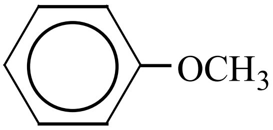
Diethyl ether

CH_2=$CHCH_2$–O–CH_3

Allyl methyl ether

CH_2=CH–O–CH=CH_2

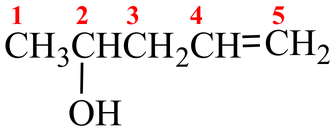
Divinyl ether



Methyl phenyl ether (Anisole)

11.1A Nomenclature of Alcohols

1. The hydroxyl group has precedence over double bonds and triple bonds in deciding which functional group to name as the suffix.



4-Penten-2-ol

2. In common radicofunctional nomenclature alcohols are called **alkyl alcohols** such as methyl alcohol, ethyl alcohol, isopropyl alcohol, and so on.

11.1B Nomenclature of Ethers

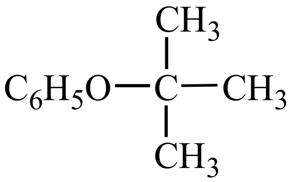
1. Simple ethers are frequently given common radicofunctional names.
   1) Simply lists (in alphabetical order) both groups that are attached to the oxygen atom and adds the word ***ether***.

$CH_3CH_2–O–CH_3$

Ethyl methyl ether

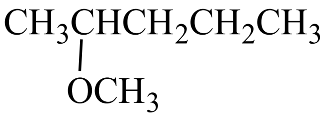
$CH_3CH_2–O–CH_2CH_3$

Diethyl ether

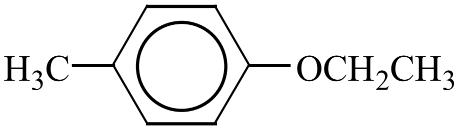


***tert*-Butyl phenyl ether**

2. IUPAC substitutive names are used for more complicated ethers and for compounds with more than one ether linkage.
   1) Ethers are named as alkoxyalkanes, alkoxyalkenes, and alkoxyarenes.
   2) The RO– group is an **alkoxy** group.



2-Methoxypentane



1-Ethoxy-4-methylbenzene

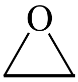
$CH_3–O–CH_2CH_2–O–CH_3$

1,2-Dimethoxyethane

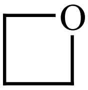
3. Cyclic ethers can be names in several ways.
   1) **Replacement nomenclature:** relating the cyclic ether to the corresponding

hydrocarbon ring system and use the prefix **oxa-** to indicate that an oxygen atom replaces a CH_2 group.

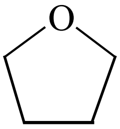
2) **Oxirane:** a cyclic three-membered ether (epoxide).
3) **Oxetane:** a cyclic four-membered ether.
4) **Common names:** given in parentheses.



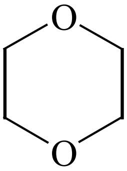
Oxacyclopropane or oxirane (ethylene oxide)



Oxacyclobutane or oxetane



Oxacyclopentane (tertahydrofuran)



1,4-Dioxacyclohexane (1,4-dioxane)

4. Tetrahydrofuran (THF) and 1,4-dioxane are useful solvents.

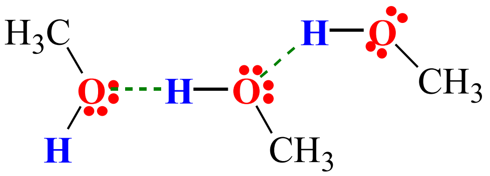
11.2 Physical Properties of Alcohols and Ethers

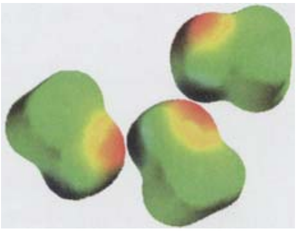
1. Ethers have boiling points that are comparable with those of hydrocarbons of the same molecular weight.
   1) The b.p. of diethyl ether (MW = 74) is 34.6 °C; that of pentane (MW = 74) is 36 °C.

2. Alcohols have much higher b.p. than comparable ethers or hydrocarbons.
   1) The b.p. of butyl alcohol (MW = 74) is 117.7 °C.
   2) The molecules of alcohols can associate with each other through **hydrogen bonding**, whereas those of ethers and hydrocarbons cannot.

3. **Ethers are able to form hydrogen bonds** with compounds such as water.
   1) Ethers have solubilities in water that are similar to those of alcohols of the same molecular weight and that are very different from those of hydrocarbons.

2) Diethyl ether and 1-butanol have the same solubility in water, approximately 8 g per 100 mL at room temperature. Pentane, by contrast, is virtually insoluble in water.





Hydrogen bonding between molecules of methanol

Table 11.1 Physical Properties of Ethers

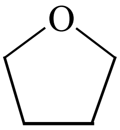
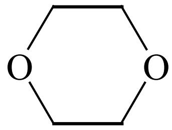
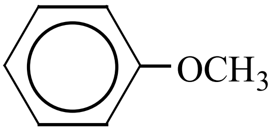
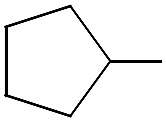
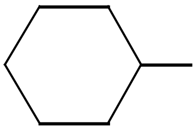
NAME	FORMULA	mp (°C)	bp (°C)	Density d_4^{20} (g mL^{-1})
Dimethyl ether	CH_3OCH_3	–138	–24.9	0.661
Ethyl methyl ether	$CH_3OCH_2CH_3$		10.8	0.697
Diehyl ether	$CH_3CH_2OCH_2CH_3$	–116	34.6	0.714
Dipropyl ether	$(CH_3CH_2CH_2)_2O$	–122	90.5	0.736
Diisopropyl ether	$(CH_3)_2CHOCH(CH_3)_2$	–86	68	0.725
Dibutyl ether	$(CH_3CH_2CH_2CH_2)_2O$	–97.9	141	0.769
1,2-Dimethoxyethane	$CH_3OCH_2CH_2OCH_3$	–68	83	0.863
Tetrahydrofuran		–108	65.4	0.888
1,4-Dioxane		11	101	1.033
Anisole (methoxybenzene)		–37.3	158.3	0.994

Table 11.2 Physical Properties of Alcohols

Compound	Name	mp (°C)	bp(°C) (1 atm)	Density d_4^{20} (g mL^{-1})	Water Solubility (g 100 mL^{-1} H_2O)
Monohydroxy Alcohols					
CH_3OH	Methanol	–97	64.7	0.792	∞
CH_3CH_2OH	Ethanol	–117	78.3	0.789	∞
$CH_3CH_2CH_2OH$	Propyl alcohol	–126	97.2	0.804	∞
$CH_3CH(OH)CH_3$	Isopropyl alcohol	–88	82.3	0.786	∞
$CH_3CH_2CH_2CH_2OH$	Butyl alcohol	–90	117.7	0.810	8.3
$CH_3CH(CH_3)CH_2OH$	Isobutyl alcohol	–108	108.0	0.802	10.0
$CH_3CH_2CH(OH)CH_3$	*sec*-Butyl alcohol	–114	99.5	0.808	26.0
$(CH_3)_3COH$	*tert*-Butyl alcohol	25	82.5	0.789	∞
$CH_3(CH_2)_3CH_2OH$	Pentyl alcohol	–78.5	138.0	0.817	2.4
$CH_3(CH_2)_4CH_2OH$	Hexyl alcohol	–52	156.5	0.819	0.6
$CH_3(CH_2)_5CH_2OH$	Heptyl alcohol	–34	176	0.822	0.2
$CH_3(CH_2)_6CH_2OH$	Octyl alcohol	–15	195	0.825	0.05
$CH_3(CH_2)_7CH_2OH$	Nonyl alcohol	–5.5	212	0.827	
$CH_3(CH_2)_8CH_2OH$	Decyl alcohol	6	228	0.829	
$CH_2{=}CHCH_2OH$	Allyl alcohol	–129	97	0.855	∞
OH	Cyclopentanol	–19	140	0.949	
OH	Cyclohexanol	24	161.5	0.962	3.6
$C_6H_5CH_2OH$	Benzyl alcohol	–15	205	1.046	4
Diols and Triols					
CH_2OHCH_2OH	Ethylene glycol	–12.6	197	1.113	∞
$CH_3CHOHCH_2OH$	Propylene glycol	–59	187	1.040	∞
$CH_2OHCH_2CH_2OH$	Trimethylene glycol	–30	215	1.060	∞
$CH_2OHCHOHCH_2OH$	Glycerol	18	290	1.261	∞

4. Methanol, ethanol, both propanols, and *tert*-butyl alcohol are completely miscible with water.
   1) The remaining butyl alcohols have solubilities in water between 8.3 and 26.0 g per 100 mL.
   2) The solubility of alcohols in water gradually decreases as the hydrocarbon portion of the molecule lengthens.

11.3 IMPORTANT ALCOHOLS AND ETHERS

11.3A METHANOL

1. At one time, most methanol was produced by the destructive distillation of wood (i.e., heating wood to a high temperature in the absence of air) ⇒ "wood alcohol".
   1) Today, most methanol is prepared by the catalytic hydrogenation of carbon monoxide.

$$CO + 2\,H_2 \xrightarrow[\text{200-300 atm, } ZnO\text{-}Cr_2O_3]{300\text{-}400^{\circ}C} CH_3OH$$

2. Methanol is highly toxic ⇒ ingestion of small quantities of methanol can cause blindness; large quantities cause death.
   1) Methanol poisoning can also occur by inhalation of the vapors or by prolonged exposure to the skin.

11.3B ETHANOL

1. Ethanol can be made by fermentation of sugars, and it is the alcohol of all alcoholic beverages.
   1) Sugars from a wide variety of sources can be used in the preparation of alcoholic beverages.
   2) Often, these sugars are from grains ⇒ "grain alcohol".

2. Fermentation is usually carried out by adding yeast to a mixture of sugars and water.

   1) Yeast contains enzymes that promote a long series of reactions that ultimately convert a simple sugar ($C_6H_{12}O_6$) to ethanol and carbon dioxide.

$$C_6H_{12}O_6 \xrightarrow{\text{yeast}} 2\ CH_3CH_2OH + 2\ CO_2$$

   2) Enzymes of the yeast are deactivated at higher ethanol concentrations ⇒ fermentation alone does not produce beverages with an ethanol content greater than 12-15%.

   3) To produce beverages of higher alcohol content (brandy, whiskey, and vodka) the aqueous solution must be distilled.

   4) The "proof" of an alcoholic beverage is simply twice the percentage of ethanol (by volume) ⇒ 100% proof whiskey is 50% ethanol.

   5) The flavors of the various distilled liquors result from other organic compounds that distill with the alcohol and water.

3. An **azeotrope** of 95% ethanol and 5% water boils at a lower temperature (78.15°C) than either pure ethanol (bp 78.3°C) or pure water (bp 100°C).

   1) Azeotrope can also have boiling points that are higher than that of either of the pure components.

   2) Benzene forms an **azeotrope** with ethanol and water that is 7.5% water which boils at 64.9°C ⇒ allows removal of the water from 95% ethanol.

   3) Pure ethanol is called **absolute alcohol**.

4. Most ethanol for industrial purposes is produced by the acid-catalyzed hydration of ethene.

$$CH_2{=}CH_2 + H_2O \xrightarrow[\text{Acid}]{} CH_3CH_2OH$$

5. Ethanol is a ***hypnotic*** (sleep producer).

   1) Ethanol depresses activity in the upper brain even though it gives the illusion of being a stimulant.

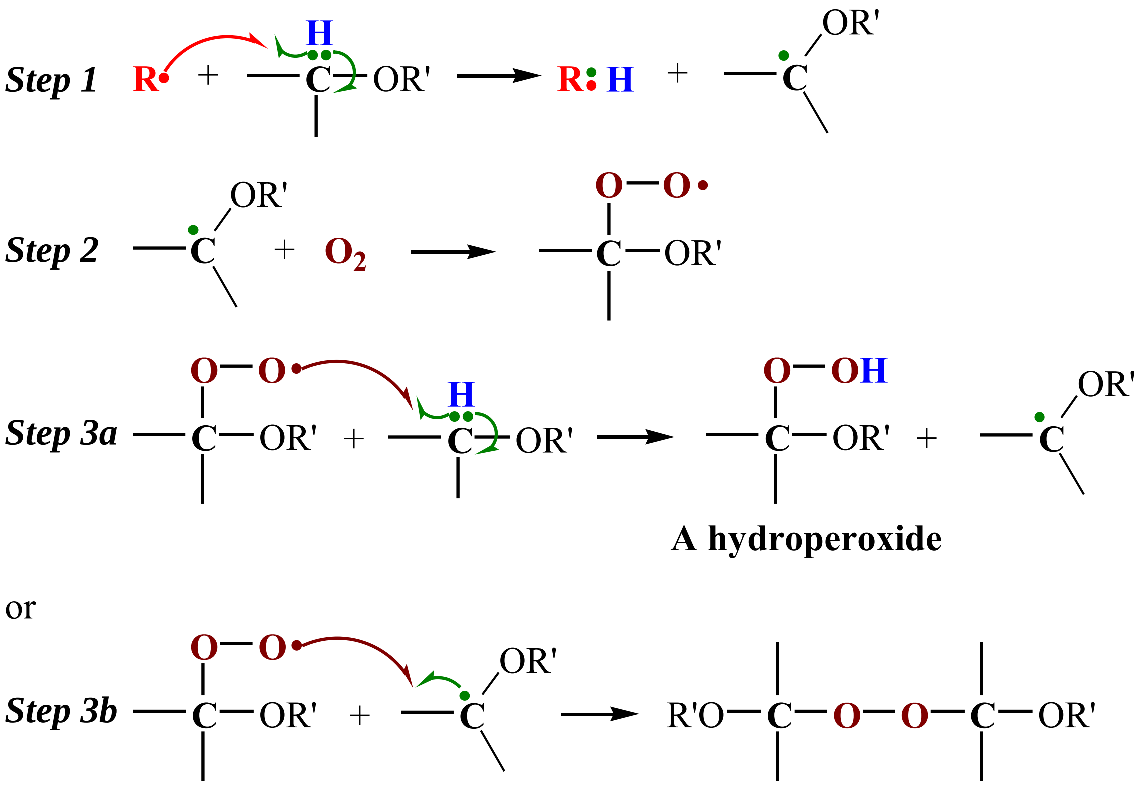
2) Ethanol is toxic. In rats the lethal dose of ethanol is 13.7 g/Kg of body weight.
3) Abuse of ethanol is a major drug problem in most countries.

11.3C ETHYLENE GLYCOL

1. Ethylene glycol ($HOCH_2CH_2OH$) has a low molecular weight and a high boiling point and is miscible with water ⇒ ethylene glycol is an ideal automobile antifreeze.
   1) Ethylene glycol is toxic.

11.3D DIETHYL ETHER

1. Diethyl ether is a very low-boiling, highly flammable liquid ⇒ open flames or sparks from light switches can cause explosive combustion of mixture of diethyl ether and air.
2. Most ethers react slowly with oxygen by a radical process called **autooxidation** to form hydroperoxides and peroxides.



3. These hydroperoxides and peroxides, which often accumulate in ethers that have been left standing for long periods in contact with air, are dangerously explosive.

1) They often detonate without warning when ether solutions are distilled to near dryness ⇒ **test for** and **decompose** any ether peroxides before a distillation is carried out.

4. Diethyl ether was first used as a surgical anesthetic by C. W. Long of Jefferson, Georgia, in 1842 and shortly after by J. C. Waren of the Massachusetts General Hospital in Boston.

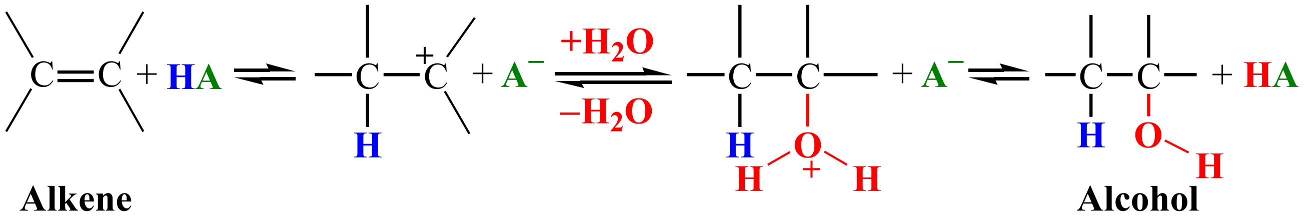
1) The most popular modern anesthetic is halothane ($CF_3CHBrCl$). Halothane is not flammable.

11.4 SYNTHESIS OF ALCOHOLS FROM ALKENES

1. **Acid-Catalyzed Hydration of Alkenes:**

1) Water adds to alkenes in the presence of an acid catalyst following **Markovnikov's rule**.

i) The reaction is reversible.



2) Because **rearrangements** often occur, the **acid-catalyzed hydration of alkenes** has **limited usefulness** as a laboratory method.

2. **Oxymercuration-Demercuration:**

1) Oxymercuration-demercuration gives **Markovnikov** addition of **H–** and **–OH** to an alkene, yet it is **not complicated by rearrangement**.

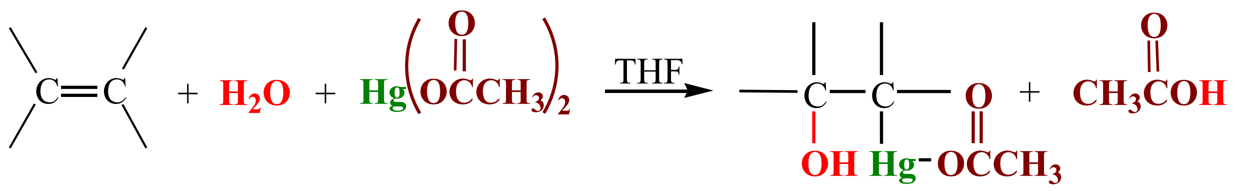
3. **Hydroboration-Oxidation:**

1) Hydroboration-oxidation gives **anti-Markovnikov** but syn addition of **H–** and **–OH** to an alkene.

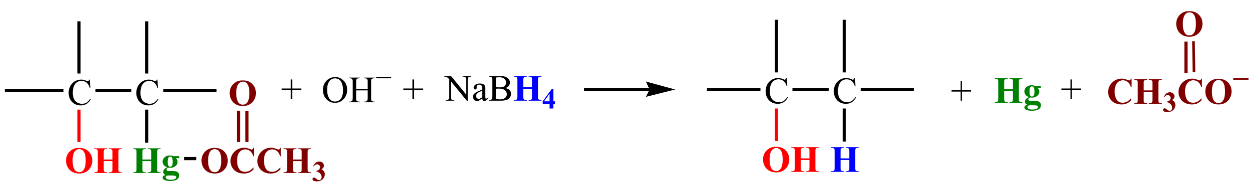
11.5 ALCOHOLS FROM ALKENES THROUGH OXYMERCURATION-DEMERCURATION

1. Alkenes react with $Hg(OAc)_2$ in a mixture of THF and water to produce (hydroxyalkyl)mercury compounds.
2. The (hydroxyalkyl)mercury compounds can be reduced to alcohols with $NaBH_4$.

***Step 1*: Oxymercuration**

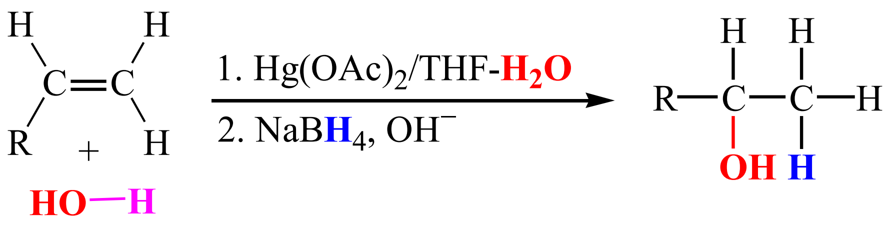


***Step 2*: Demercuration**

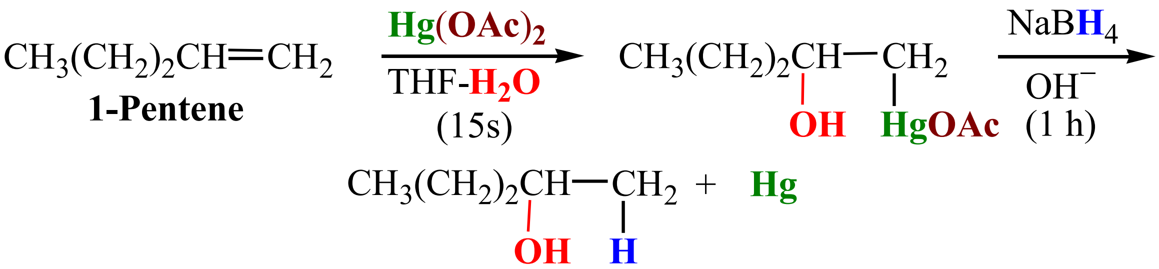


3. Both steps can be carried out in the same vessel, and both reactions take place very rapidly at room temperature or below.
   1) Oxymercuration usually goes to completion within a period of 20 s to 10 min.
   2) Demercuration normally requires less than an hour.
   3) The overall reaction gives alcohols in very high yields, usually greater than 90%.

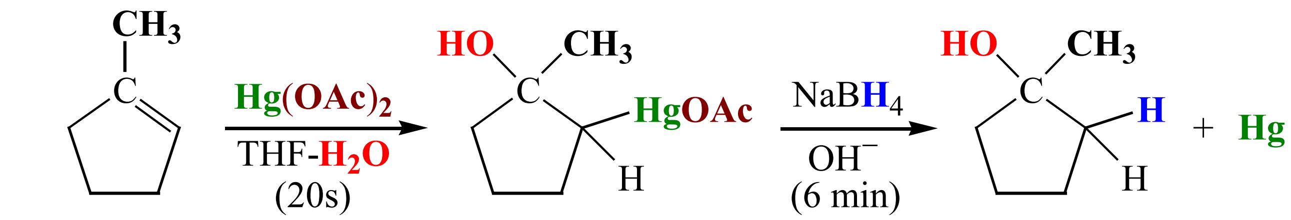
4. Oxymercuration-demercuration **is highly regioselective**.
   1) The H– becomes attached to the carbon atom of the double with the greater number of hydrogen atoms:



5. Specific examples:

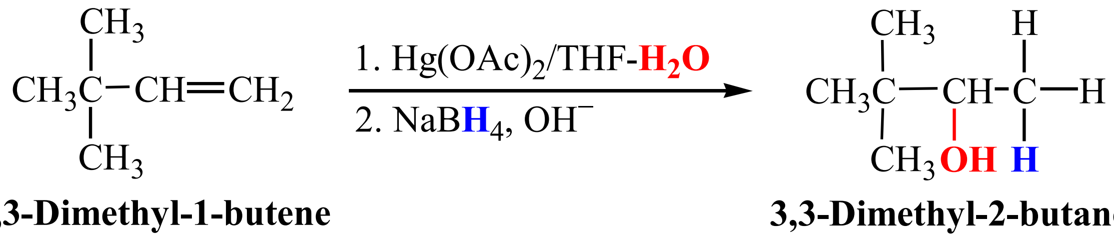


2-Pentanol (93%)



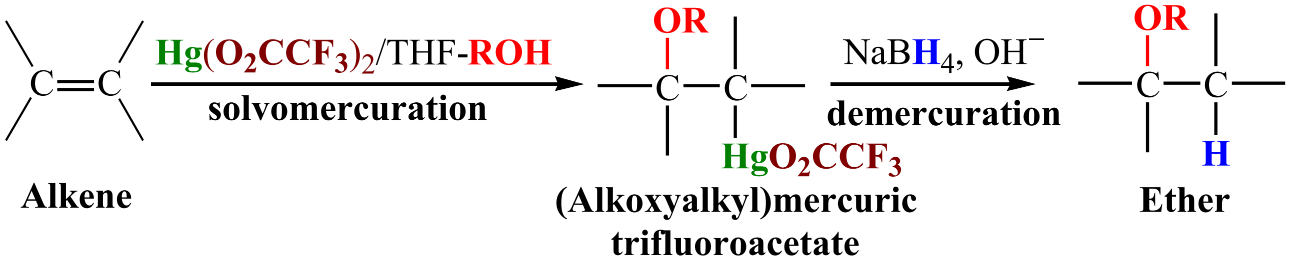
1-Methylcyclo-pentene **1-Methylcyclo-pentanol**

6. **Rearrangements** of the carbon skeleton seldom occur in oxymercuration-demercuration.



1) 2,3-Dimethyl-2-butanol can not be detected by gas chromatography (GC) analysis.
2) 2,3-Dimethyl-2-butanol is the major product in the acid-catalyzed hydration of 3,3-dimethyl-1-butene.

7. **Solvomercuration-demercuration:**



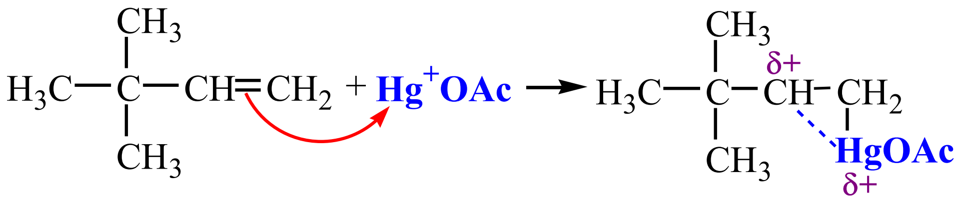
A Mechanism for the Reaction

Oxymercuration

Step 1 $Hg(OAc)_2 \rightleftharpoons {}^{+}HgOAc + {}^{-}OAc$

Mercuric acetate dissociates to form an $Hg^{+}OAc$ ion and an acetate ion.

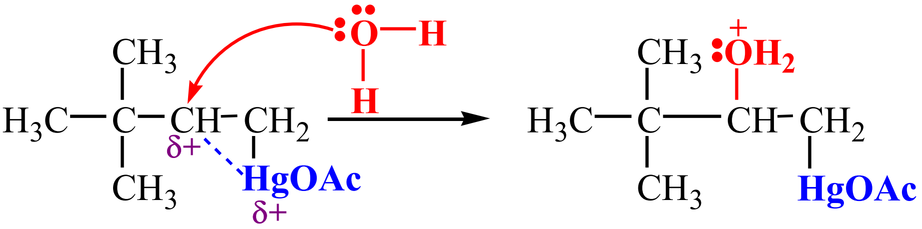
Step 2



3,3-Dimethyl-1-butene **Mercury-bridged carbocation**

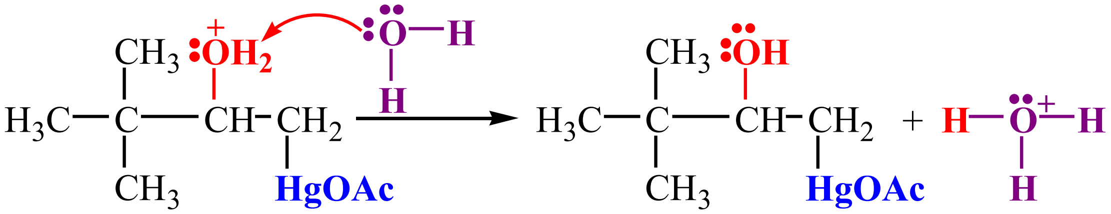
The electrophilic $HgOAc^{+}$ ion accepts a pair of electrons from the alkene to form a mercury-bridged carbocation. In this carbocation, the positive charge is shared between the 2° carbon atom and the mercury atom. The charge on the carbon atom is large enough to account for the Markovnikov orientation of the addition, but not large enough for a rearrangement to occur.

Step 3



A water molecule attacks the carbon bearing the partial positive charge.

Step 4



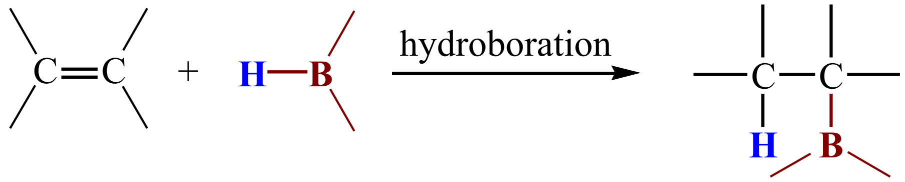
(Hydroxyalkyl)mercury compound

An acid-base reaction transfers a proton to another water molecule (or to an acetate ion). This step produces the (hydroxyalkyl)mercury compound.

8. **Mercury compounds are extremely hazardous.**

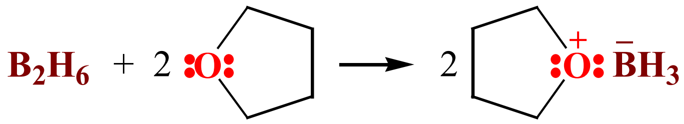
11.6 HYDROBORATION: SYNTHESIS OF ORGANOBORANES

1. **Hydroboration**, discovered by Herbert C. Brown of Purdue University (co-winner of the Nobel Prize for Chemistry in 1979), involves an addition of a H–B bond (a **boron hydride**) to an alkene.



Alkene **Boron hydride** **Organoborane**

2. Hydroboration can be carried out by using the boron hydride (B_2H_6) called **diborane**.
   1) It is much more convenient to use a THF solution of diborane.



Diborane **THF** **THF : BH_3**

BH_3 is a Lewis acid (because the boron has only six electrons in its valence shell). It accepts an electron pair from the oxygen atom of THF.

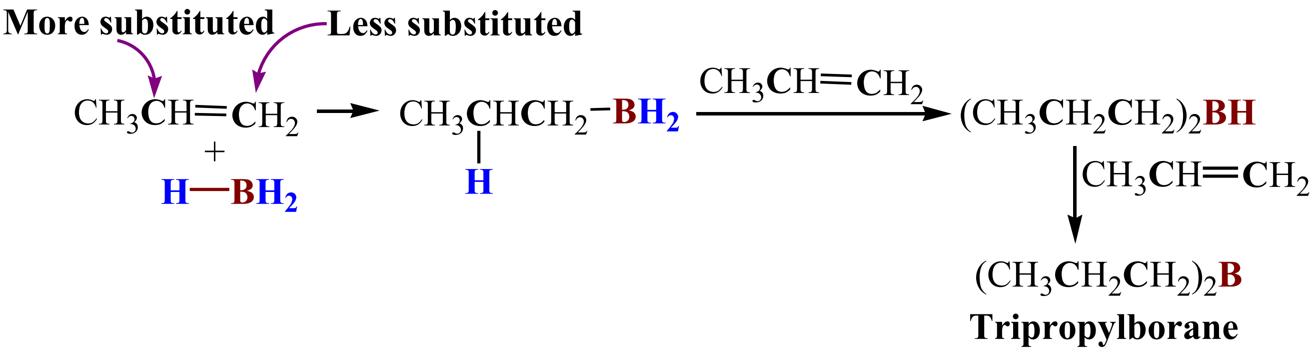
   2) Solutions containing the THF:BH_3 complex is commercially available.
   3) Hydroboration reactions are usually carried out in ether: either in $(C_2H_5)_2O$, or in some higher molecular weight ether such as "**diglyme**" [$(CH_3OCH_2CH_2)_2O$, ***di***ethylene ***gly***col di***me***thyl ether].

3. **Great care must be used in handling diborane and alkylboranes because they ignite spontaneously in air (with a green flame). The solution of THF:BH_3 is considerably less prone to spontaneous ignition but still must be used in an inert atmosphere and with care**.

11.6A MECHANISM OF HYDROBORATION

1. When an 1-alkene is treated with a solution containing the THF:BH_3 complex, the

boron hydride adds successively to the double bonds of three molecules of the alkene to form a trialkylborane:



2. The **boron atom** becomes **attached to the less substituted carbon atom** of the double bond.

1) Hydroboration is **regioselective** and is **anti-Markovnikov**.

2) The observed **regioselectivity** of hydroboration results in part from **steric factors** — the bulky boron-containing group can approach the less substituted carbon atom more easily.

3. Mechanism of hydroboration:

1) In the first step, the π electrons of the double bond adds to the vacant *p* orbital of BH_3.

2) In the second step, the π complex becomes the addition product by passing through a four-center transition state in which the boron atom is partially bonded to the less substituted carbon atom of the double bond.

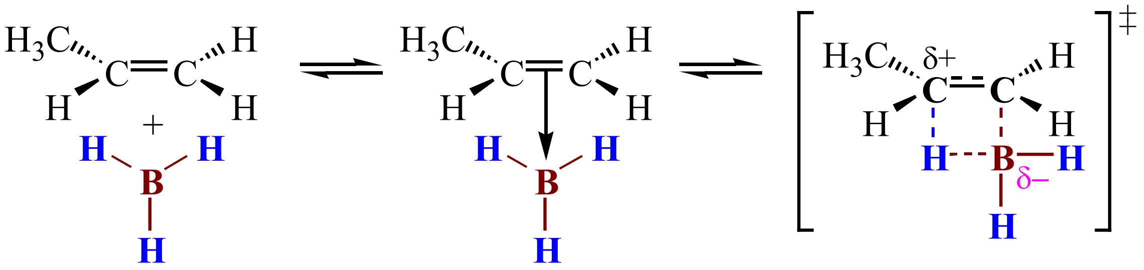
i) Electrons shift in the direction of the boron atom and away from the more substituted carbon atom of the double bond.

ii) This makes the more substituted carbon atom develop a partial positive charge, and because ***it bears an electron-releasing alkyl group, it is better able to accommodate this positive charge***.

3) Both ***electronic*** and ***steric factors*** accounts for the anti-Markovnikov orientation of the addition.

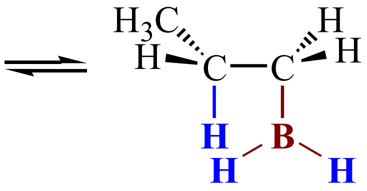
A Mechanism for the Reaction

Hydroboration



π complex **Four-center transition state**

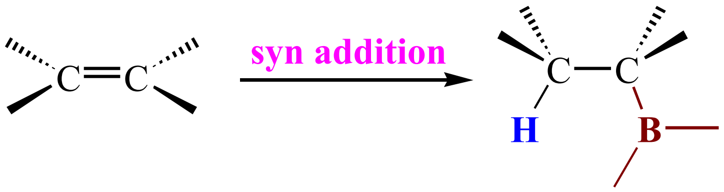
Addition takes place through the initial formation of a π complex, which changes into a cyclic four-center transition state with the boron atom adding to the less hindered carbon atom. The dashed bonds in the transition state represent bonds that are partially formed or partially broken.

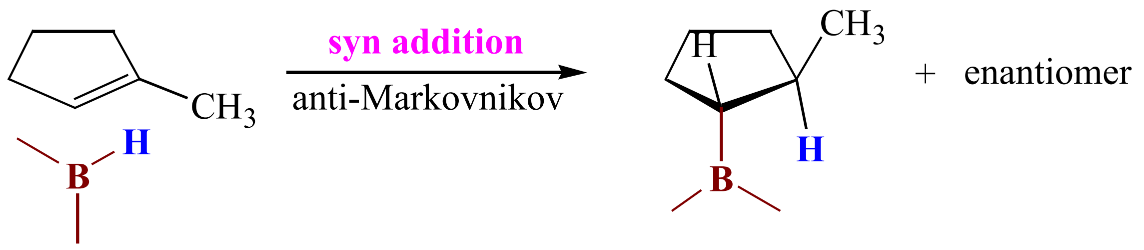


The transition state passes over to become an alkylborane. The other B–H bonds of the alkylborane can undergo similar additions, leading finally to a trialkylborane.

11.6B THE STEREOCHEMISTRY OF HYDROBORATION

1. The transition state for the hydroboration requires that the ***boron atom*** and the ***hydrogen atom*** **add to the same face of the double bond** ⇒ **a *syn* addition**.





11.7 ALCOHOLS FROM ALKENES THROUGH HYDROBORATION-OXIDATION

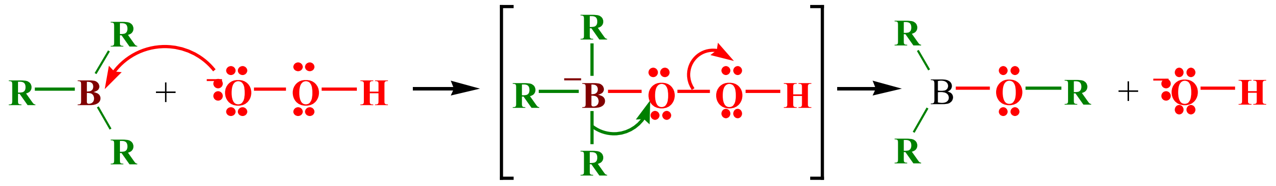
1. Addition of the elements of water to a double bond can be achieved through **hydroboration**, followed by **oxidation** and **hydorlysis** of the **organoboron** intermediate to an alcohol and boric acid.

$$3\,CH_3CH{=}CH_2 \xrightarrow[\text{Hydroboration}]{\text{THF:BH}_3} (CH_3CH_2CH_2)_3B \xrightarrow[\text{Oxidation}]{H_2O_2/OH^-} 3\,CH_3CH_2CH_2OH$$

Propene **Tripropylborane** **Propyl alcohol**

A Mechanism for the Reaction

Oxidation of Trialkylboran



Trialkyl-borane **Hydroperoxide ion** **Unstable intermediate** **Borate ester**

The boron atom accepts an electron pair from the hydroperoxide ion to form an unstable intermediate.

An alkyl group migrates from boron to the adjacent oxygen atom as a hydroxide ion depatrs.

2. The **alkylborane** produced in the **hydroboration**, without isolation, are **oxidized** and **hydrolyzed** to alcohols in the same reaction vessel by the addition of hydrogen peroxide in aqueous base.

$$R_3B \xrightarrow[\text{NaOH, 25 °C}]{H_2O_2} 3\ R{-}OH + Na_3BO_3$$

oxidation

3. The **alkyl migration** takes place ***with retention of configuration of the alkyl group*** which leads to the formation of a trialkyl borate, an ester, $B(OR)_3$.

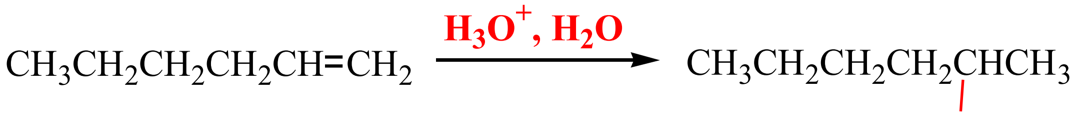
   1) The ester then undergoes basic hydrolysis to produce three molecules of alcohol and a borate ion.

$$B(OR)_3 + 3\ OH^- \xrightarrow{H_2O} 3\ R{-}OH + BO_3^{3-}$$

4. The net result of **hydroboration-oxidation** is an **anti-Markovnikov addition of water** to a double bond.

5. Two complementary orientations for the addition of water to a double bond:

   1) Acid-catalyzed hydration (or oxymercuration-demercuration) of 1-hexene:



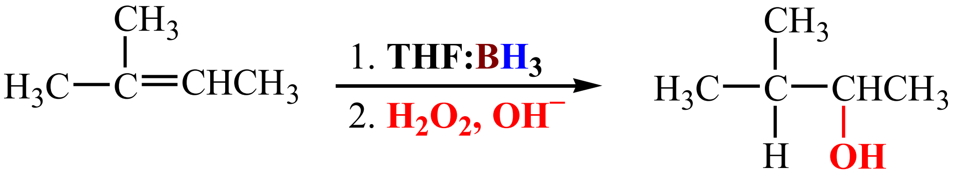
1-Hexene **2-Hexanol**

   2) **Hydroboration-oxidation** of 1-hexene:

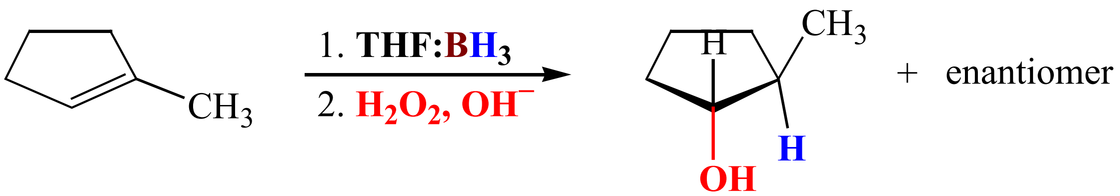
$$CH_3CH_2CH_2CH_2CH{=}CH_2 \xrightarrow[\text{2. } H_2O_2,\ OH^-]{\text{1. THF:}BH_3} CH_3CH_2CH_2CH_2CH_2CH_2OH$$

1-Hexene **1-Hexanol (90%)**

   3) Other examples of **hydroboration-oxidation** of alkenes:



2-Methyl-2-butene **3-Methyl-2-butanol (59%)**



1-Methylcyclopentene ***trans*-2-Methylcyclopentanol (86%)**

11.7A The Stereochemistry of Hydroboration

1. The net result of **hydroboration-oxidation** is a **syn addition** of –H and –OH to a double bond.

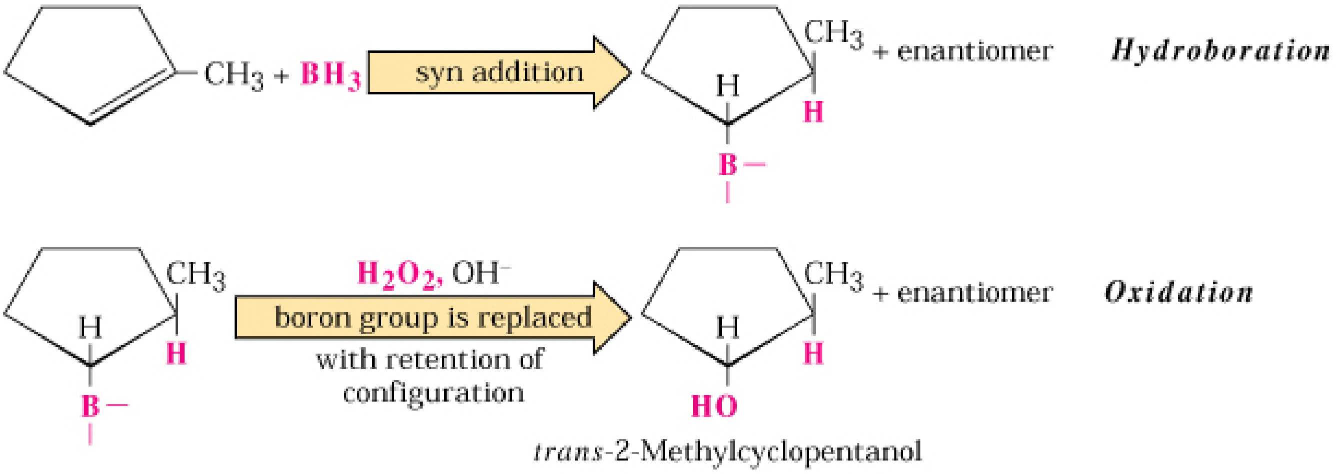
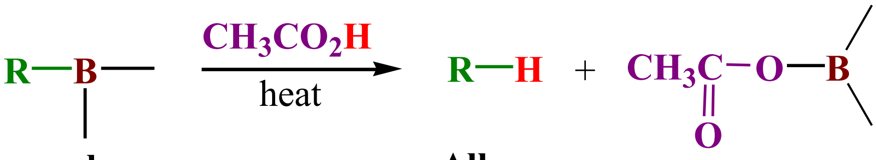


Figure 11.1 **The hydroboration-oxidation of 1-methylcyclopentene. The first reaction is a syn addition of borane. (In this illustration we have shown the boron and hydrogen both entering from the bottom side of 1-methylcyclopentene. The reaction also takes place from the top side at an equal rate to produce the enantiomer.) In the second reaction the boron atom is replaced by a hydroxyl group with retention of configuration. The product is a trans compound (*trans*-2-methyl-cyclopentanol), and the overall result is the *syn* addition of –H and –OH.**

11.7B Protonolysis of Organoboranes

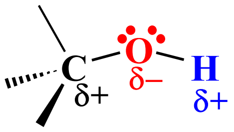
1. Heating an organoborane with acetic acid causes cleavage of the C–B bond:
   1) This reaction also takes place with retention of configuration ⇒ the stereochemistry of the reaction is like that of the oxidation of organoboranes ⇒ it can be very useful in introducing deuterium or tritium in a specific way.

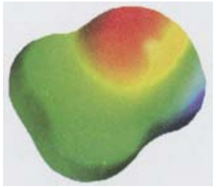


Organoborane Alkane

11.8 REACTIONS OF ALCOHOLS

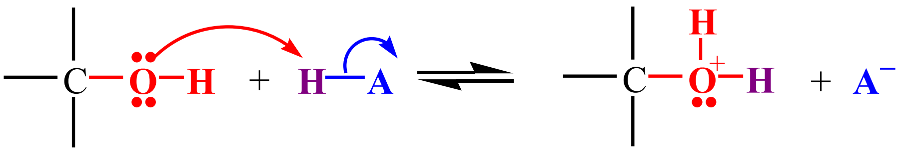
1. The oxygen atom of an alcohol polarizes both the C–O bond and the O–H bond:





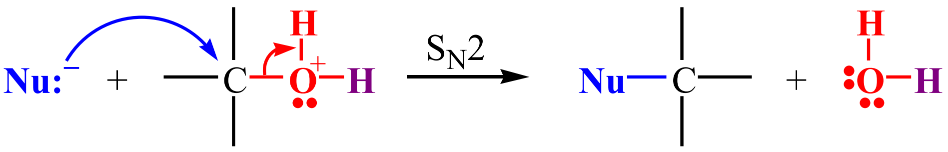
The functional group of an alcohol **An electrostatic potential map for methanol**

1) Polarization of the O–H bond makes the hydrogen partially positive ⇒ alcohols are weak acids.
2) The OH^- is a strong base ⇒ OH^- is a very poor leaving group.
3) The electron pairs on the oxygen atom make it both ***basic*** and ***nucleophilic***.
   i) In the presence of strong acids, alcohols act as bases and accept protons:



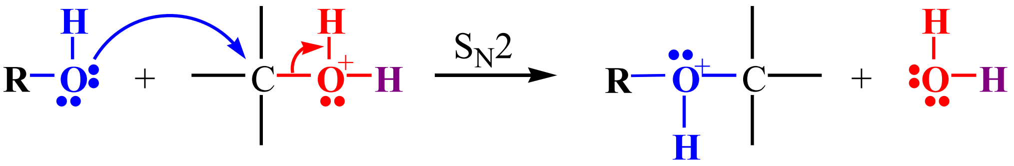
Alcohol **Strong acid** **Protonated alcohol**

2. Protonation of the alcohol converts a poor leaving group (OH^-) into a good one (H_2O).
   1) It also makes the carbon atom even more positive (because $-OH_2^+$ is more electron withdrawing than –OH) ⇒ the carbon atom is more susceptible to nucleophilic attack ⇒ Substitution reactions become possible (S_N2 or S_N1, depending on the class of alcohol).



Protonated alcohol

2) Alcohols are nucleophiles ⇒ they can react with protonated alcohols to afford ethers.



Protonated alcohol **Protonated ether**

3) At a high enough temperature, and in the absence of a good nucleophile, protonated alcohols are capable of undergoing E1 or E2 reactions.

11.9 ALCOHOLS AS ACIDS

1. Alcohols have acidities similar to that of water.

1) Methanol is a slightly stronger acid than water but most alcohols are somewhat weaker acids.

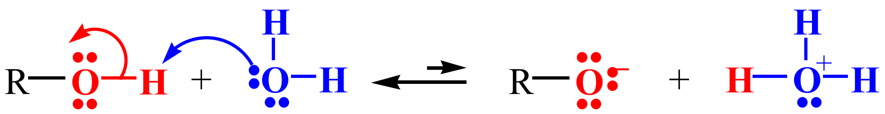
Table 11.3 **pK_a Values for Some Weak Acids**

Acid	pK_a
CH_3OH	15.5
H_2O	15.74
CH_3CH_2OH	15.9
$(CH_3)_3COH$	18.0

2) The lesser acidity of sterically hindered alcohols such as *tert*-butyl alcohol arises from solvation effects.

i) With unhindered alcohols, water molecules are able to surround and solvate the

negative oxygen of the alkoxide ion formed ⇒ solvation stabilizes the alkoxide ion and increases the acidity of the alcohol.



Alcohol **Alkoxide ion (stablized by solution)**

ii) If the R– group of the alcohol is bulky, solvation of the alkoxide ion is hindered ⇒ the alkoxide ion is not so effectively stabilized ⇒ the alcohol is a weaker acid.

2. Relative acidity of acids:

Relative Acidity

$$H_2O > ROH > RC{\equiv}CH > H_2 > NH_3 > RH$$

Relative Basicity

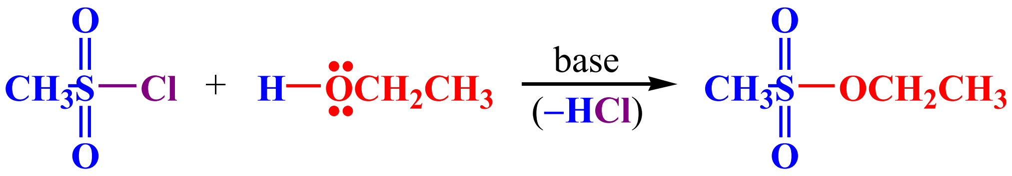
$$R^- > NH_2^- > H^- > RC{\equiv}C^- > RO^- > HO^-$$

3. Sodium and potassium alkoxides are often used as **bases** in organic synthesis.

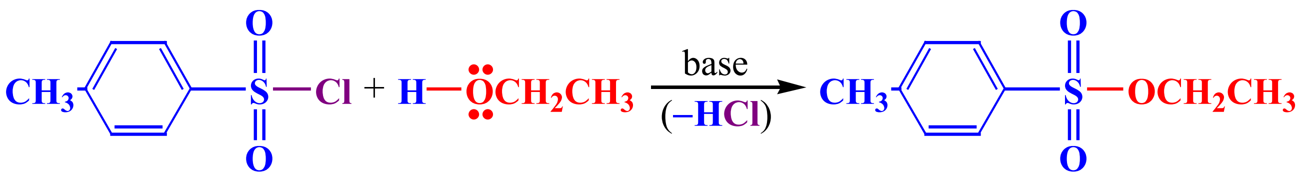
11.10 Conversion of Alcohols into Mesylates and Tosylatess

1. Alcohols react with sulfonyl chlorides to form **sulfonates**.

1) These reactions involve cleavage of the O–H bond of the alcohol and not the C–O bond ⇒ no change of configuration would have occurred if the alcohol had been chiral.



Methanesulfonyl chloride **Ethanol** **Ethyl methanesulfonate (ethyl mesylate)**

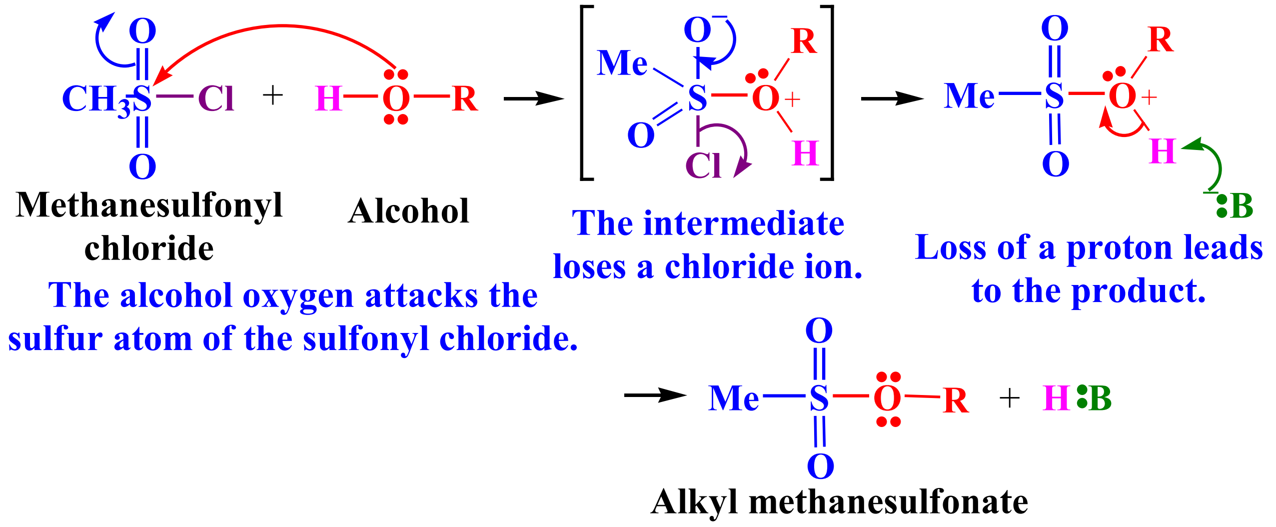


p-Toluenesulfonyl chloride — Ethanol — Ethyl *p*-toluenesulfonate (ethyl tosylate)

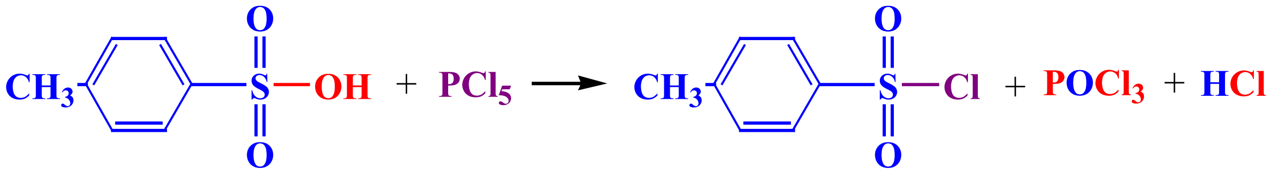
2. The mechanism for the **sulfonation** of alcohols:

A Mechanism for the Reaction

Conversion of an Alcohol into an Alkyl Methanesulfonate



3. Sulfonyl chlorides are usually prepared by treating sulfonic acids with phosphorus pentachloride.

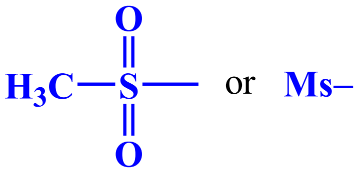


p-Toluenedulfonic acid — *p*-toluenesulfonyl chloride (tosyl chloride)

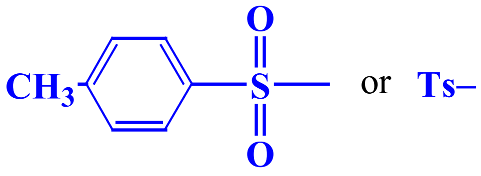
4. Abbreviations for methanesulfonyl chloride and *p*-toluenesulfonyl chloride are "**mesyl chloride**" and "**tosyl chloride**", respectively.
   1) Methanesulfonyl group is called a "**mesyl**" group and *p*-toluenesulfonyl group is

called a “**tosyl**” group.

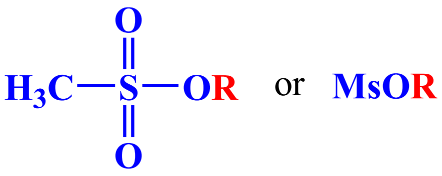
2) Methanesulfonates are known as “**mesylates**” and *p*-toluenesulfonates are known as “**tosylates**”.



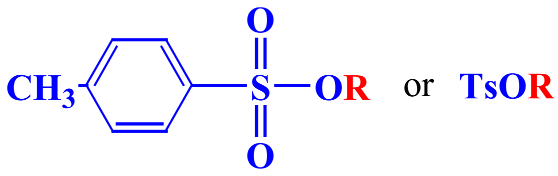
The mesyl group



The tosyl group



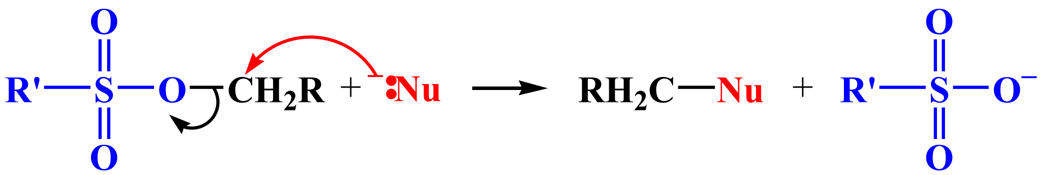
An alkyl mesylate



An alkyl tosylate

11.11 MESYLATES AND TOSYLATES IN S_N2 REACTIONS

1. Alkyl sulfonates are frequently used as substrates for nucleophilic substitution reactions.



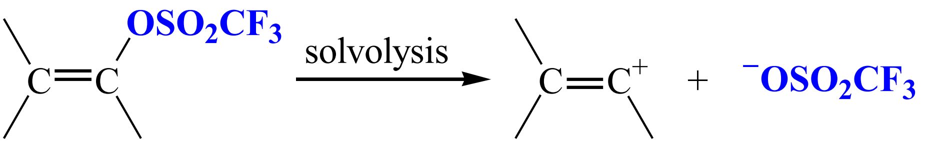
Alkyl sulfonate
(tosylate, mesylate, etc.)

Sulfonate ion
(very weak base ––– a good leaving group)

2. The trifluoromethanesulfonate ion ($CF_3SO_2O^-$) is one of the best of all known leaving groups.

1) Alkyl trifluoromethanesulfonates — called ***alkyl triflates*** — react extremely rapidly in nucleophilic substitution reactions.

2) The triflate ion is such a good leaving group that even vinylic triflatres undergo S_N1 reactions and yield vinylic cations.

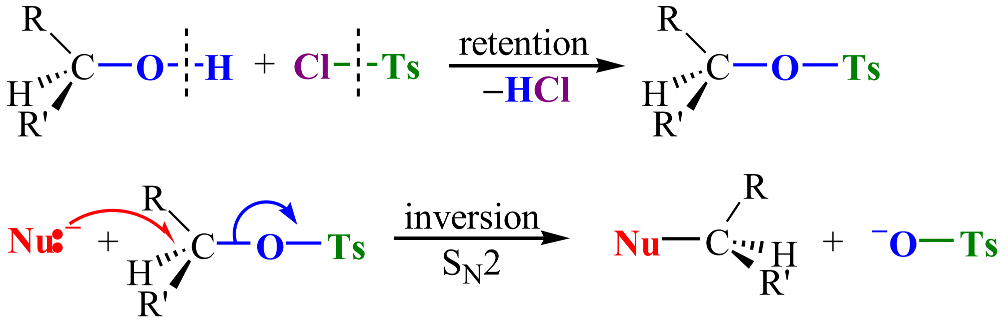


Vinylic triflate **Vinylic cation** **Triflate ion**

3. Alkyl sulfonates provide an indirect method for carrying out nucleophilic substitution reactions on alcohols.

Step 1

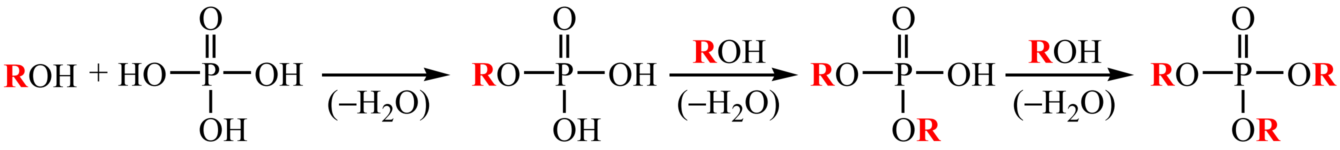
Step 2



1) The alcohol is converted to an alkyl sulfonate first and then the alkyl sulfonate is reacted with a nucleophile.
2) The first step — sulfonate formation — proceeds with **retention of configuration** because no bonds to the stereocenter are broken.
3) The second step — if the reaction is S_N2 — proceeds with **inversion of configuration**.
4) Allkyl sulfonates undergo all the nucleophilic substitution reactions that alkyl halides do.

The Chemistry of Alkyl Phosphates

1. Alcohols react with phosphoric acid to yield alkyl phosphates:



Phosphoric acid **Alkyl dihydrogen phosphate** **Dialkyl hydrogen phosphate** **Trialkyl phosphate**

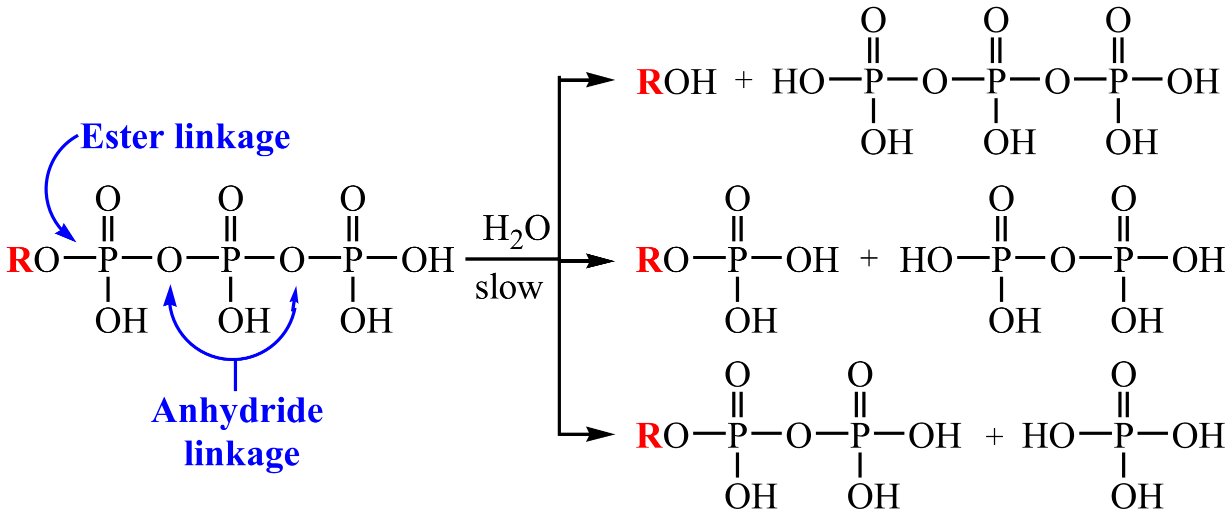
1) Esters of phosphoric acids are important in biochemical reactions (triphosphate

esters are especially important).

2) Although hydrolysis of the ester group or of one of the anhydride linkages of an alkyl triphosphate is exothermic, these reactions occur very slowly in aqueous solutions.

3) Near pH 7, these phosphates exist as negatively charged ions and hence are much less susceptible to nucleophilic attack ⇒ Alkyl triphosphates are relatively stable compounds in the aqueous medium of a living cell.

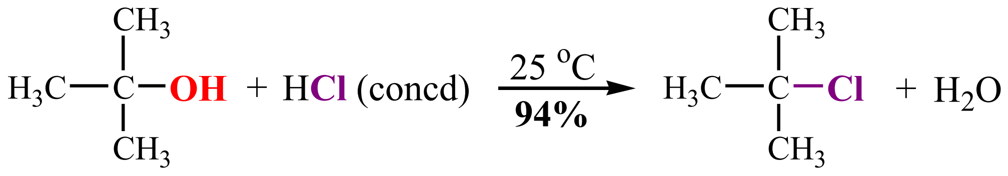
2. Enzymes are able to catalyze reactions of these triphosphates in which the energy made available when their anhydride linkages break helps the cell make other chemical bonds.



11.12 Conversion of Alcohols into Alkyl Halides

1. Alcohols react with a variety of reagents to yield alkyl halides.

1) Hydrogen halides (HCl, HBr, or HI):

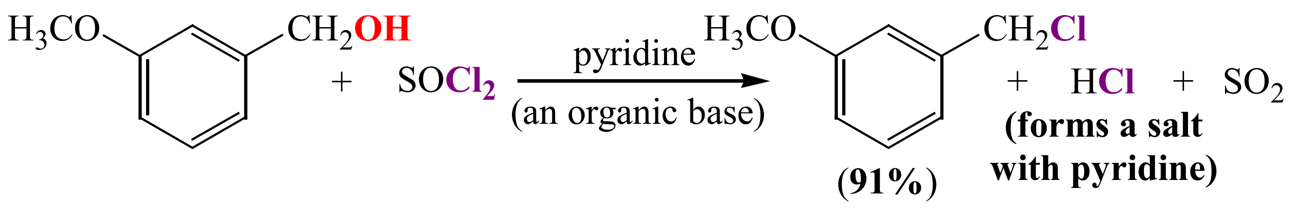


$$CH_3CH_2CH_2CH_2OH + HBr\ (concd) \xrightarrow[\text{reflux}]{} CH_3CH_2CH_2CH_2Br\ (95\%)$$

2) Phosphorous tribromide (PBr_3):

$$3\,(CH_3)_2CHCH_2OH + PBr_3 \xrightarrow[4\text{ h}]{-10\text{ to }0\,^{\circ}C} 3\,(CH_3)_2CHCH_2Br + H_3PO_3$$
$$(55\text{-}60\%)$$

3) Thionyl chloride ($SOCl_2$):



11.13 Alkyl Halides From the Reaction of Alcohols with Hydrogen Halides

1. When alcohols react with a HX, a substitution takes place producing an RX and H_2O:

$$R\text{-}OH + HX \longrightarrow R\text{—}X + H_2O$$

   1) The order of reactivity of the **HX** is: **HI** > **HBr** > **HCl** (**HF** is generally unreactive).
   2) The order of reactivity of **alcohols** is: **3° > 2° > 1° < methyl**.

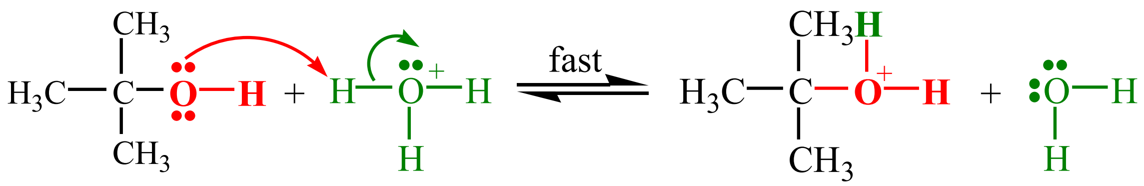
2. The reaction is acid catalyzed.

$$ROH + NaX \xrightarrow{H_2SO_4} RX + NaHSO_4 + H_2O$$

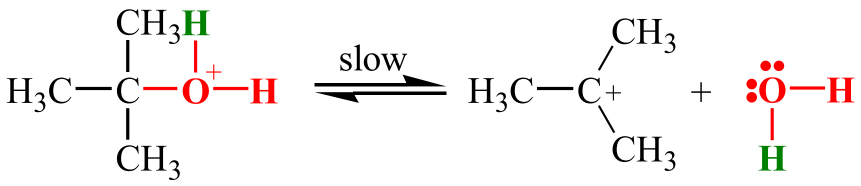
11.13A Mechanisms of the Reactions of Alcohols with HX

1. 2°, 3°, allylic, and benzylic alcohols appear to react by an S_N1 mechanism.
   1) **The porotonated alcohol acts as the substrate**.

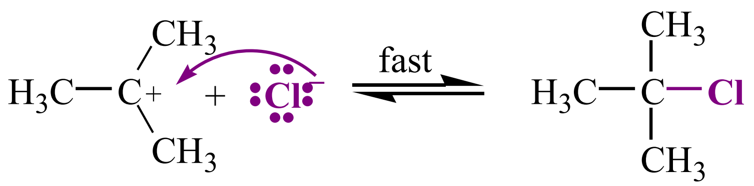
Step 1



Step 2



Step 3



i) The first two steps are the same as in the mechanism for the dehydration of an alcohol ⇒ the alcohol accepts a proton and then the protonated alcohol dissociates to form a **carbocation** and water.

ii) In step 3, the carbocation reacts with a nucleophile (a halide ion) in an S_N1 reaction.

2. Comparison of dehydration and RX formation from alcohols:

1) Dehydration is usually carried out in concentrated sulfuric acid.

i) The only nucleophiles present in the reaction mixture are water and hydrogen sulfate (HSO_4^-) ions.

ii) Both are poor nucleophiles and both are usually present in low concentrations ⇒ The highly reactive carbocation stabilizes itself by losing a proton and becoming an alkene ⇒ an E1 reaction.

2) Conversion of an alcohol to an alkyl halide is usually carried out in the presence of acid and ***in the presence of halide ions***.

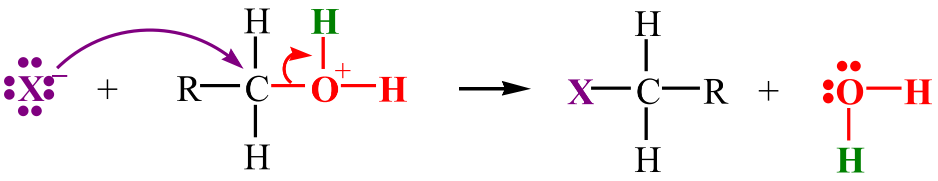
i) The only nucleophiles present in the reaction mixture are water and hydrogen sulfate (HSO_4^-) ions.

ii) Halide ions are good nucleophiles and are present in high concentrations ⇒ Most of the carbocations stabilize themselves by accepting the electron pair of a halide ion ⇒ an S_N1 reaction.

3. Dehydration and RX formation from alcohols furnish another example of the competition between nucleophilic substitution and elimination.

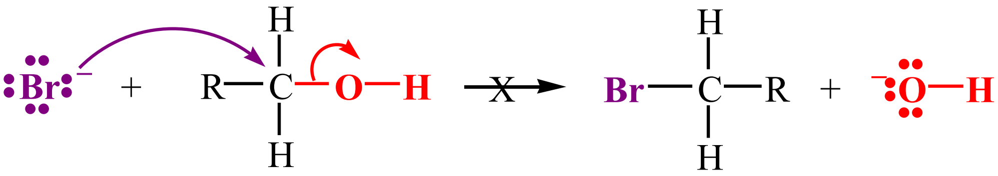
1) The free energies of activation for these two reactions of carbocations are not very different from one another.
2) In conversion of alcohols to alkyl halides (substitution), very often, the reaction is accompanied by the formation of some alkenes (elimination).

4. Acid-catalyzed conversion of 1° alcohols and methanol to alkyl halides proceeds through an ***S*** S_N2 mechanism.



(**protonated 1° alcohol or methanol**) (**a good leaving group**)

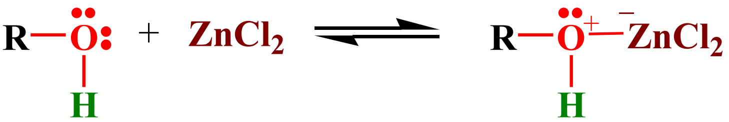
1) Although halide ions (particularly I^- and Br^-) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols directly.

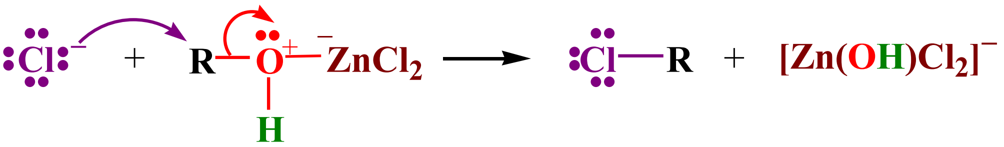


5. Many reactions of alcohols, particularly those in which carbocations are formed, ***are accompanied by rearrangements***.

6. Chloride ion is a weaker nucleophile than bromide and iodide ions ⇒ chloride does not react with 1° or 2° alcohols unless zinc chloride or some Lewis acid is added to the reaction.

1) $ZnCl_2$, a good Lewis acid, forms a complex with the alcohol through association with an lone-pair electrons on the oxygen ⇒ provides a better leaving group for the reaction than H_2O.





$$[Zn(OH)Cl_2]^- + H^+ \rightleftharpoons ZnCl_2 + H_2O$$

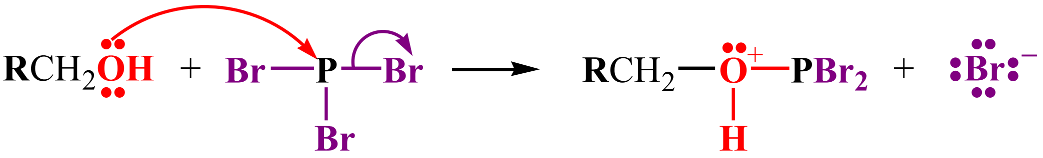
11.14 Alkyl Halides From the Reaction of Alcohols with PBr_3 or $SOCl_2$

1. 1° and 2° alcohols react with phosphorous tribromide to yield alkyl bromides.

$$3\ R\text{-}OH + PBr_3 \longrightarrow 3\ R\text{—}Br + H_3PO_3$$
$$(1^o \text{or } 2^o)$$

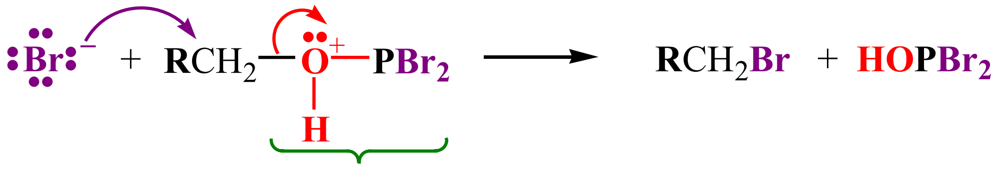
   1) The reaction of an alcohol with PBr_3 does not involve the formation of a carbocation and ***usually occurs without rearrangement*** ⇒ PBr_3 is often preferred for the formation of an alcohol to the corresponding alkyl bromide.

2. The mechanism of the reaction involves the initial formation of a protonated alkyl dibromophosphite by a nucleophilic displacement on phosphorus:



Protonated alkyl dibromophosphite

   1) Then a bromide ion acts as a nucleophile and displaces $HOPBr_2$.



A good leaving group

      i) The $HOPBr_2$ can react with more alcohol ⇒ 3 mol of alcohol is converted to 3 mol of alkyl bromide by 1 mol of PBr_3.

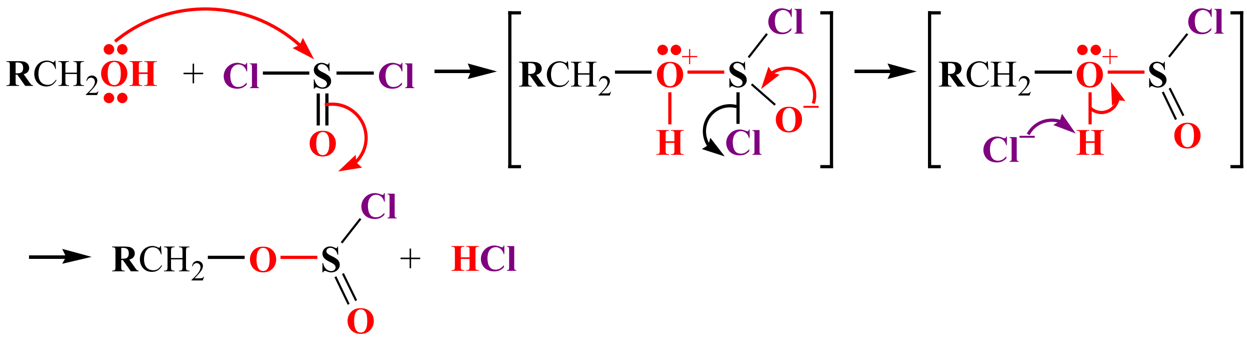
3. Thionyl chloride ($SOCl_2$) converts 1° and 2° alcohols to alkyl chlorides (usually without rearrangement):

$$\underset{(1^{o}\text{ or }2^{o})}{R{-}OH} + SOCl_2 \xrightarrow{\text{reflux}} R{-}Cl + HCl + SO_2$$

i) A 3° amine is added to promote the reaction by reacting with the HCl.

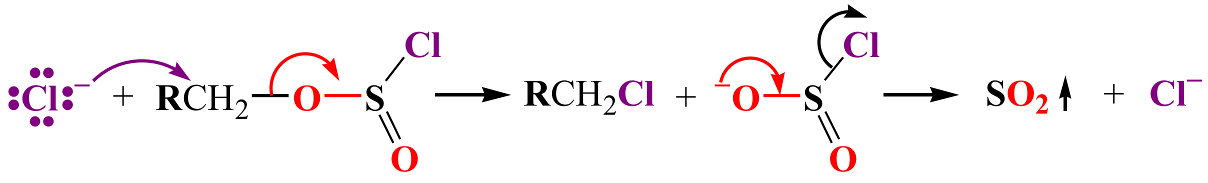
$$R_3N{:} + HCl \longrightarrow R_3NH^+ + Cl^-$$

4. The reaction mechanism involves the initial formation of the alkyl chlorosulfite:



Alkyl chlorosulfite

i) Then a chloride ion (from $R_3N{:} + HCl \longrightarrow R_3NH^+ + Cl^-$) can bring about an S_N2 displacement of a very good leaving group, $ClSO_2^-$, which, by decomposing (to SO_2 and Cl^- ion), helps drive the reaction to completion.



11.15 Synthesis of Ethers

11.15A Ethers by Intermolecular Dehydration of Alcohols

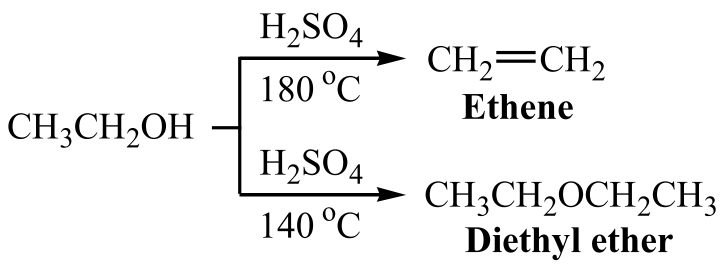
1. Alcohols can dehydrate to form alkenes.

$$R{-}OH + HO{-}R \xrightarrow[-H_2O]{H^+} R{-}O{-}R$$

1) Dehydration to an ether usually takes place at a lower temperature than dehydration to an alkene.

i) The dehydration to an ether can be aided by distilling the ether as it is formed.

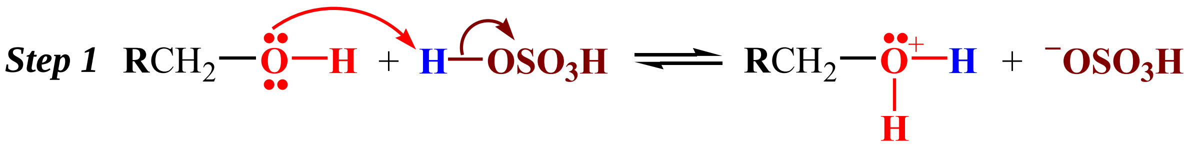
ii) Et_2O is the predominant product at 140°C; ethane is the major product at 180°C



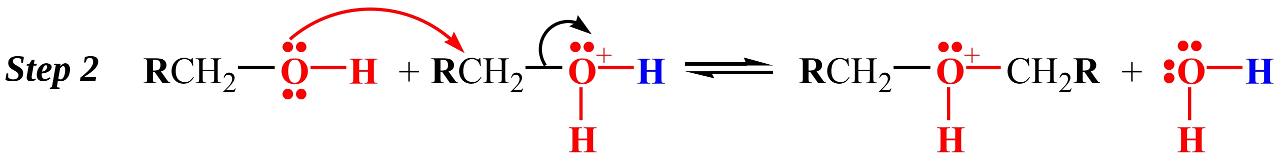
2. The formation of the ether occurs by an S_N2 mechanism with one molecule of the alcohol acting as the nucleophile and with another protonated molecule of the alcohol acting as the substrate.

A Mechanism for the Reaction

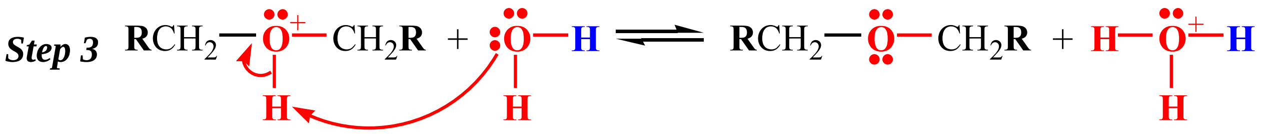
Intermolecular Dehydration of Alcohols to Form an Ether



This is an acid-base reaction in which the alcohol accepts a proton from the sulfuric acid.



Another molecule of alcohol acts as a nucleophile and attacks the protonnated alcohol in S_N2 reaction.

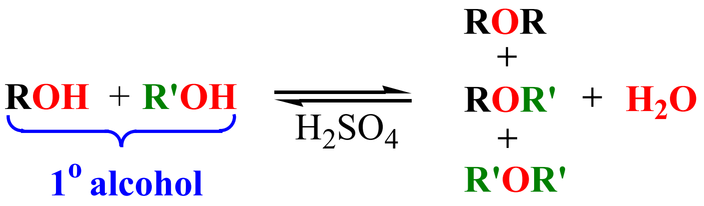


Another acid-base reaction converts the protonated ether to an ether by transferring a proton to a molecule of water (or to another molecule of alcohol).

1) Attempts to synthesize ethers with 2° alkyl groups by intermolecular dehydration

of 2° alcohols are usually unsuccessful because alkenes form too easily ⇒ This method of preparing ethers is of limited usefulness.

2) This method is not useful for the preparation of unsymmetrical ethers from 1° alcohols because the reaction leads to a mixture of products:

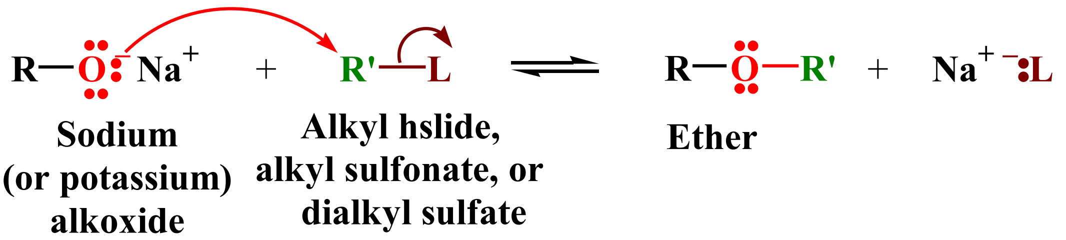


11.15B THE WILLIAMSON SYNTHESIS OF ETHERS

1. **Williamson Ether synthesis:**

A Mechanism for the Reaction

The Williamson Ether Synthesis



The alkoxide ion reacts with the substrate in an S_N2 reaction, with the resulting formation of the ether. The substrate must bear a good leaving group. Typical substrates are alkyl halides, alkyl sulfonates, and dialkyl sulfates, i.e.

$-L = -\ddot{Br}:$, $-\ddot{I}:$, $-OSO_2R''$, or $-OSO_2OR''$

2. The usual limitations of S_N2 reactions apply:

1) Best results are obtained when the alkyl halide, sulfonate, or sulfate is 1° (or methyl).

2) If the substrate is 3°, elimination is the exclusive result.

3) Substitution is favored over elimination at lower temperatures.

3. Example of Williamson ether synthesis:

$$\underset{\textbf{Propyl alcohol}}{CH_3CH_2CH_2OH} \xrightarrow{NaH} \underset{\textbf{Sodium propoxide}}{CH_3CH_2CH_2\ddot{\underset{..}{O}}{:}^{-}Na^{+}} + H{-}H$$

$$\xrightarrow[70\%]{CH_3CH_2I} \underset{\textbf{Ethyl propyl ether}}{CH_3CH_2CH_2OCH_2CH_3} + Na^{+}I^{-}$$

11.15C *TERT*-BUTYL ETHERS BY ALKTLATION OF ALCOHOLS. PROTECTING GROUPS

1. 1° alcohols can be converted to *tert*-butyl ethers by dissolving them in a strong acid such as sulfuric acid and then adding isobutylene to the mixture (to minimize dimerization and polymerization of the isobutylene).

$$RCH_2OH + H_2C{=}C(CH_3)CH_3 \xrightarrow{H_2SO_4} RCH_2O{-}\underbrace{C(CH_3)_3}_{\textbf{\textit{tert}-butyl protecting group}}$$

   1) The *tert*-butyl protecting group can be removed easily by treating the ether with dilute aqueous acid.

2. Preparation of 4-pentyn-1-ol from 3-bromo-1-propanol and sodium acetylide:

   1) The strongly basic sodium acetylide will react first with the hydroxyl group.

$$\underset{\textbf{3-Bromo-1-proponal}}{HOCH_2CH_2CH_2Br} + NaC{\equiv}CH \longrightarrow NaOCH_2CH_2CH_2Br + HC{\equiv}CH$$

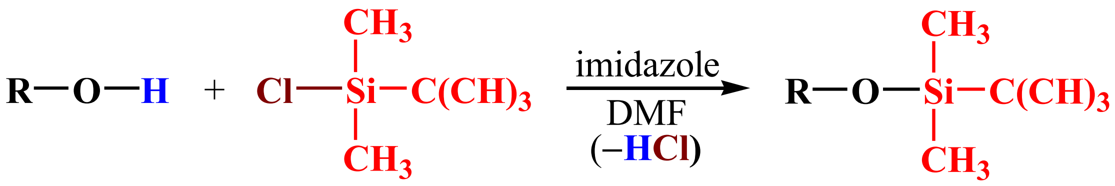
   2) The –OH group has to be protected first.

$$HOCH_2CH_2CH_2Br \xrightarrow[2.\ H_2C{=}C(CH_3)_2]{1.\ H_2SO_4} (CH_3)_3COCH_2CH_2CH_2Br \xrightarrow{NaC{\equiv}CH}$$

$$(CH_3)_3COCH_2CH_2CH_2C{\equiv}CH \xrightarrow[H_2O]{H_3O^{+}} \underset{\textbf{4-Pentyn-1-ol}}{HOCH_2CH_2CH_2C{\equiv}CH} + (CH_3)_3COH$$

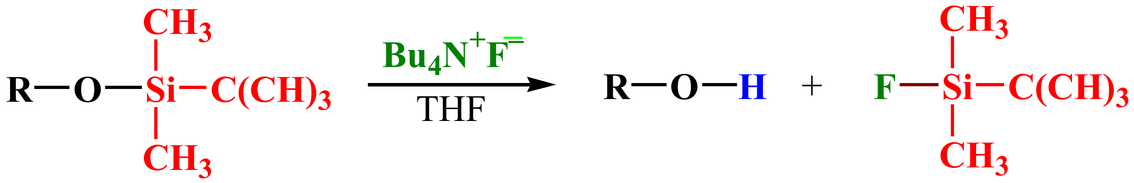
11.15D Silyl Ether Protecting Groups

1. A hydroxyl group can also be protected by converting it to a silyl ether group.
   1) *tert*-butyldimethylsilyl ether group [*tert*-butyl$(CH_3)_2$Si–O–R, or TBDMS–O–R]:
      i) Triethylsilyl, triisopropylsilyl, *tert*-butyldiphenylsilyl, and others can be used.
      ii) The *tert*-butyldimethylsilyl ether is stable over a pH range of roughly 4~12.
      iii) The alcohol is allowed to react with *tert*-butylchlorodimethylylsilane in the presence of an aromatic amine (a base) such as imidazole or pyridine.



tert-butylchlorodimethylsilane (TBDMSCl) **(R–O–TBDMS)**

      iv) The TBDMS group can be removed by treatment with fluoride ion (tetrabutylammonium fluoride):



(R–O–TBDMS)

2. Converting an alcohol to a silyl ether makes it much more volatile ⇒ can be analyzed by gas chromatography.
   1) Trimethylsilyl ethers are often used for this purpose.

11.16 Reactions of Ethers

1. Dialkyl ethers react with very few reagents other than acids.
   1) Reactive sites of a dialkyl ether: C–H bonds and –O– group.
   2) Ethers resist attack by nucleophiles and by bases.
   3) The lack of reactivity, coupled with the ability of ethers to solvate cations makes ethers especially useful as solvents for many reactions.

2. The oxygen of the ether linkage makes ethers basic ⇒ Ethers can react with proton donors to form **oxonium salts**.

$$CH_3CH_2\ddot{O}CH_2CH_3 + HBr \rightleftharpoons H_3CH_2C{-}\overset{+}{\ddot{O}}(H){-}CH_2CH_3\,Br^-$$

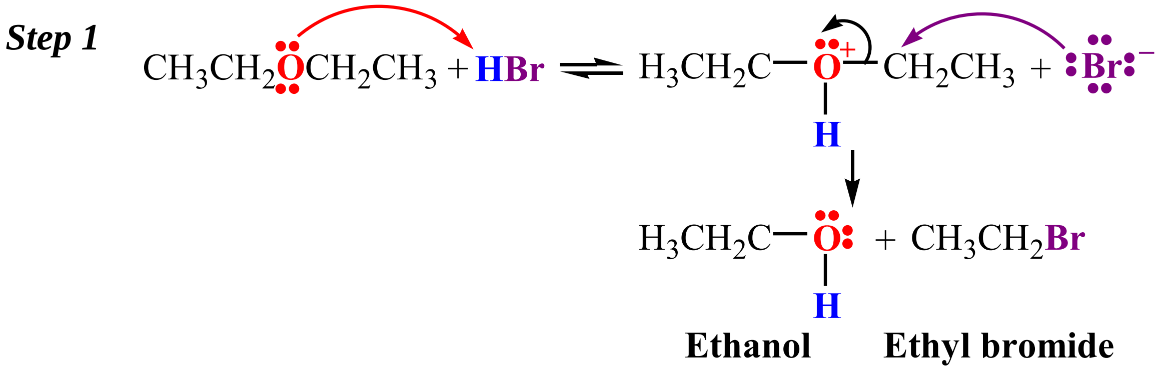
An oxonium salt

3. Heating dialkyl ethers with very strong acids (HI, HBr, and H_2SO_4) cleaves the ether linkage:

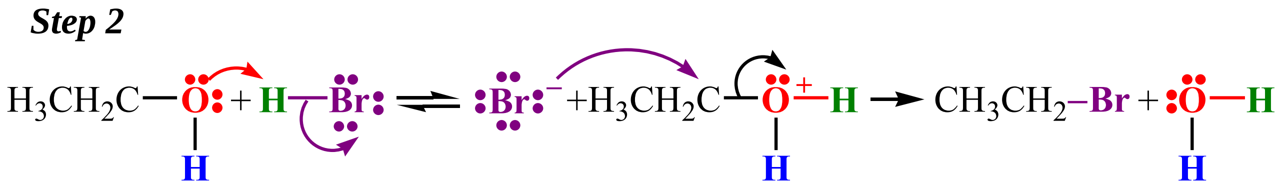
$$CH_3CH_2\ddot{O}CH_2CH_3 + 2\,HBr \longrightarrow 2\,CH_3CH_2Br + H_2O$$ **Cleavage of an ether**

A Mechanism for the Reaction

Ether Cleavage by Strong Acids



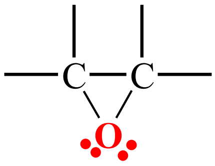
In step 2 the ethanol (just formed) reacts with HBr (present in excess) to form a second molar equivalent of ethyl bromide.



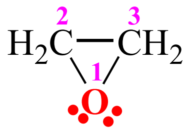
1) The reaction begins with formation of an oxonium ion.
2) An S_N2 reaction with a bromide ion acting as the nucleophile produces ethanol and ethyl bromide.
3) Excess HBr reacts with the ethanol produced to form the second molar equivalent of ethyl bromide.

11.17 EPOXIDES

1. Epoxides are cyclic ethers with three-membered rings (IUPAC: **oxiranes**).

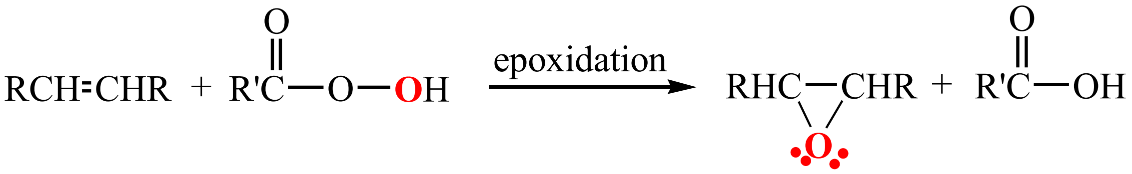


An epoxide



IUPAC nomenclature: oxirane
Common name: ethylene oxide

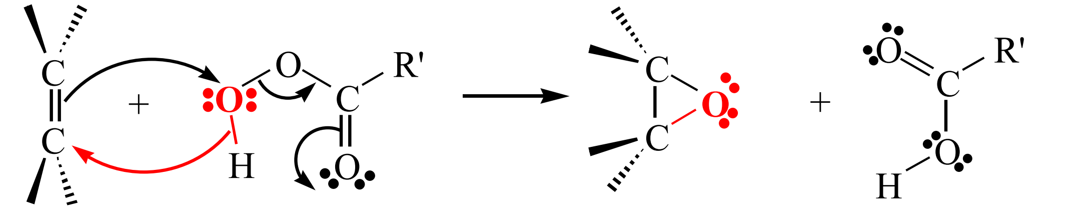
2. **Epoxidation: Syn addition**
   1) The most widely used method for synthesizing epoxides is the reaction of an alkene with an organic **peroxy acid** (**peracid**).



An alkene **A peroxy acid** **An epoxide (or oxirane)**

A Mechanism for the Reaction

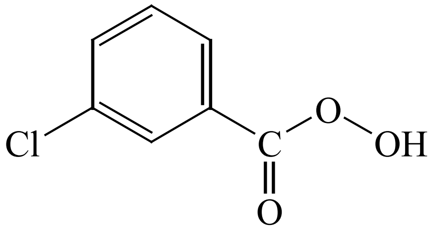
Alkene Epoxidation



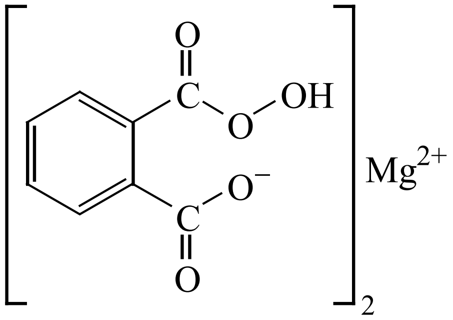
Alkene **Proxy acid** **Epoxide** **Carboxylic acid**

The peroxy acid transfers an oxygen atom to the alkene in a cyclic, single-step mechanism. The result is the syn addition of the oxygen to the alkene, with formation of an epoxide and a carboxylic acid.

3. Most often used peroxy acids for epoxidation:
   1) **MCPBA:** ***Meta*-ChloroPeroxyBenzoic Acid** (unstable).
   2) **MMPP: Magnesium MonoPeroxyPhthalate**.

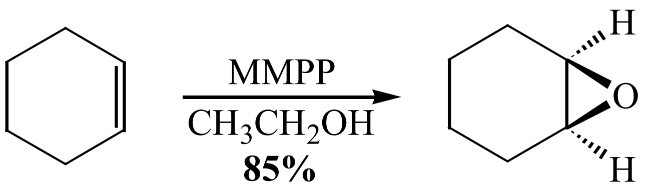


m-Chloroperoxybenzoic acid
(MCPBA)



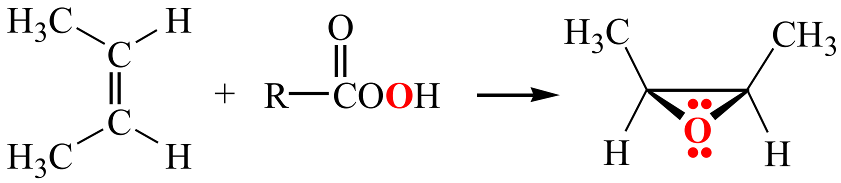
Magnesium monoperoxyphthalate
(MMPP)

4. Example:

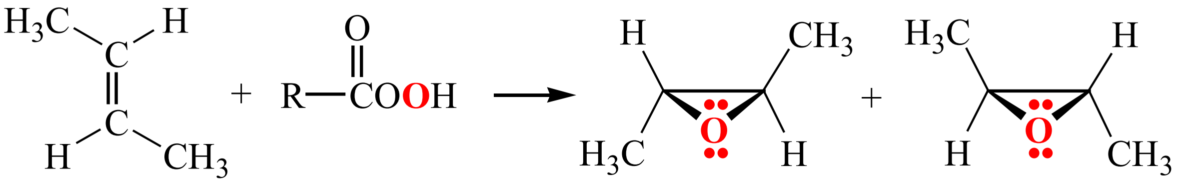


Cyclohexene **1,2-Epoxycyclohexane (cyclohexene oxide)**

5. The epoxidation of alkenes with peroxy acids is stereospecific:
   1) *cis*-2-Butene yields only *cis*-2,3-dimethyloxirane; *trans*-2-butene yields only the racemic *trans*-2,3-dimethyloxiranes.



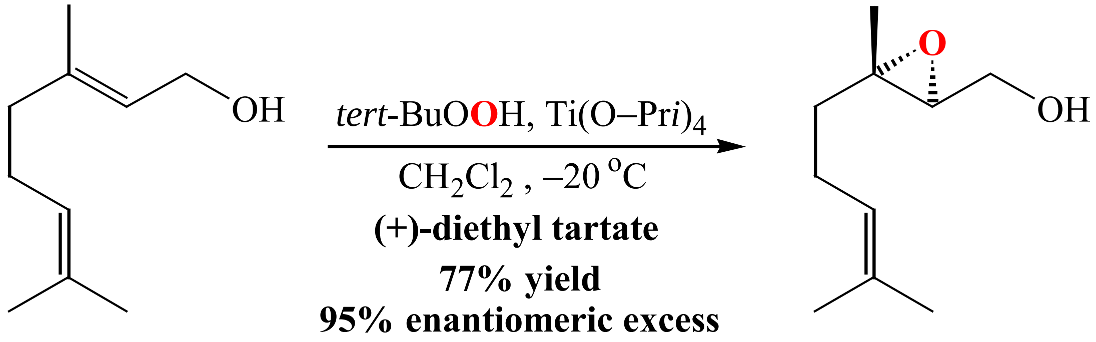
***cis*-2-Butene** ***cis*-2,3-Dimethyloxirane (a meso compound)**



***trans*-2-Butene** **Enantiomeric *trans*-2,3-dimethyloxiranes**

The Chemistry of The Sharpless Asymmetric Epoxidation

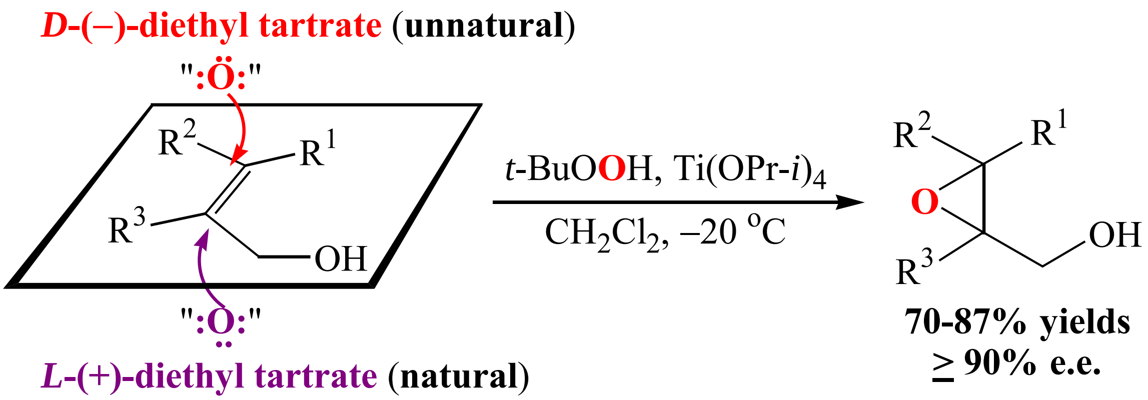
1. In 1980, K. B. Sharpless (then at the Massachusetts Institute of Technology, presently at the University of California San Diego, Scripps research Institute; co-winner of the Nobel Prize for Chemistry in 2001) and co-workers reported the "**Sharpless asymmetric epoxidation**".
2. Sharpless epoxidation involves treating an allylic alcohol with titanium(IV) tetraisopropoxide [$Ti(O–iPr)_4$], *tert*-butyl hydroperoxide [*t*-BuOOH], and a specific enantiomer of a tartrate ester.



Geraniol

3. The oxygen that is transferred to the allylic alcohol to form the epoxide is derived from *tert*-butyl hydroperoxide.

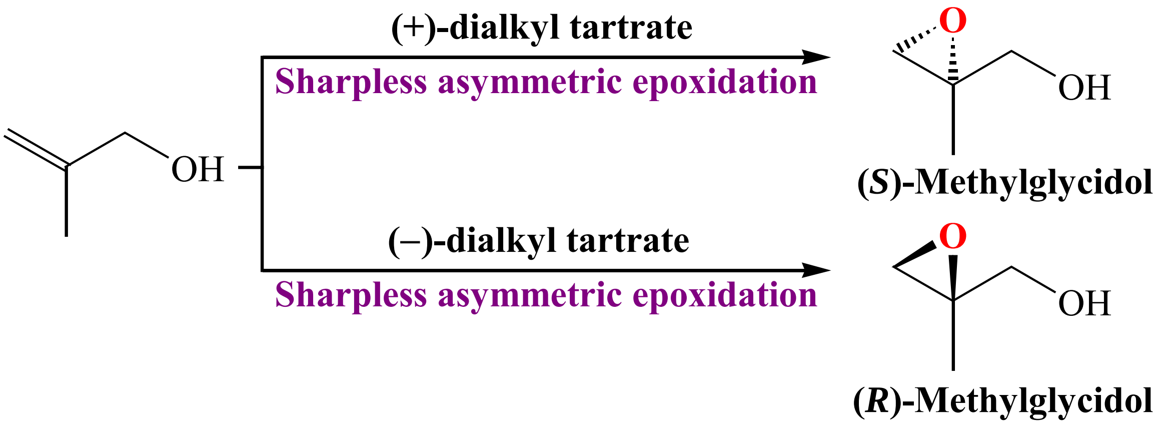
4. The enantioselectivity of the reaction results from a titanium complex among the reagents that includes the enantiomerically pure tartrate ester as one of the ligands.



"*The First Practical Methods for Asymmetric Epoxidation*"
Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

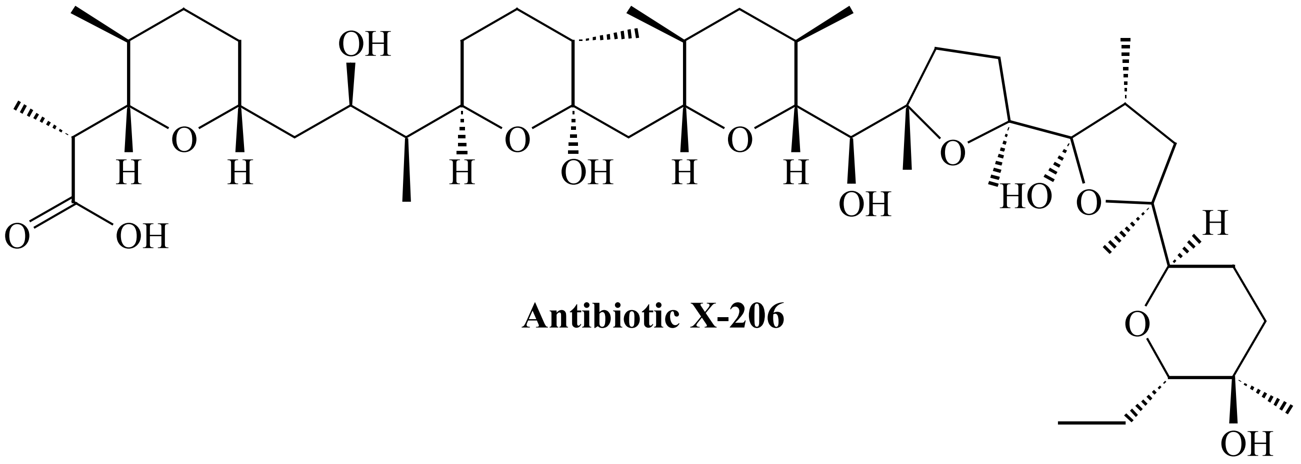
5. The tartrate (either diethyl or diisopropyl ester) stereoisomer that is chosen depends on the specific enantiomer of the epoxide desired.

1) It is possible to prepare either enantiomer of a chiral epoxide in high enantiomeric excess:



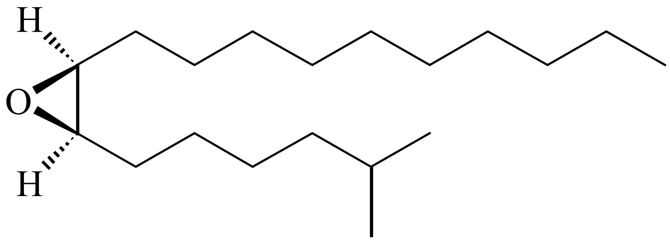
6. The synthetic utility of chiral epoxy alcohol synthons produced by the Sharpless asymmetric epoxidation has been demonstrated in enantioselective syntheses of many important compounds.

1) Polyether antibiotic X-206 by E. J. Corey (Harvard University):



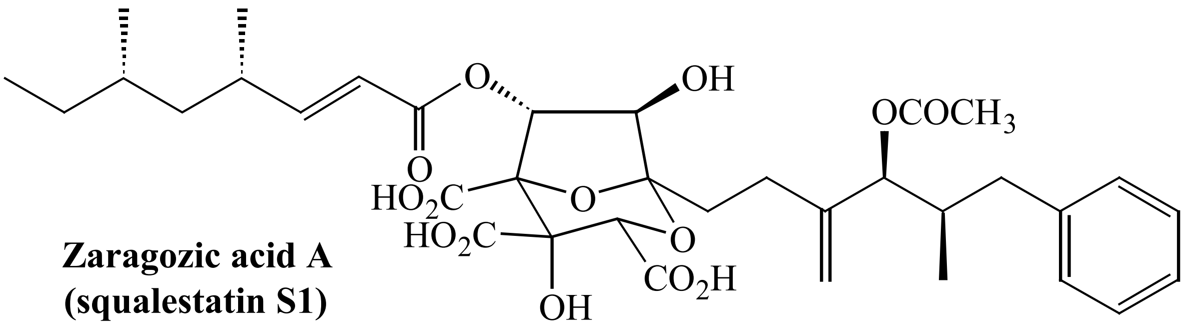
Antibiotic X-206

2) Commercial synthesis of the gypsy moth pheromone (7*R*,8*S*)-disparlure by J. T. Baker:



(7*R*,8*S*)-Disparlure

3) Zaragozic acid A (which is also called squalestatin S1 and has been shown to lower serum cholesterol levels in test animals by inhibition of squalene biosynthesis) by K. C. Nicolaou (University of California San Diego, Scripps Research Institute):

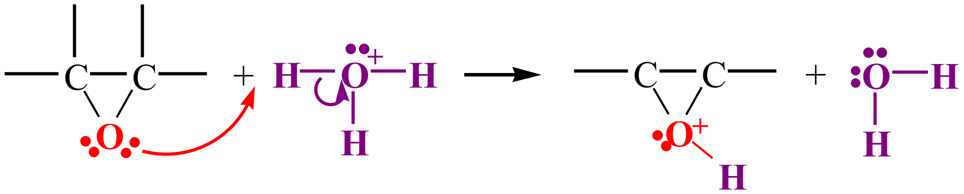


Zaragozic acid A (squalestatin S1)

11.18 REACTIONS OF EPOXIDES

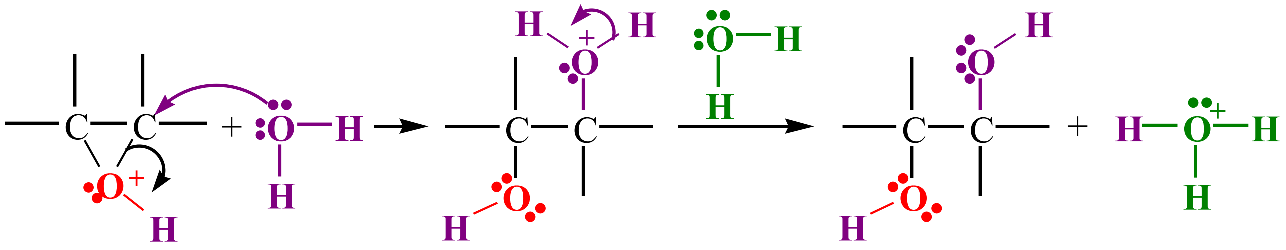
A Mechanism for the Reaction

Acid-Catalyzed Ring Opening of an Epoxide



Epoxide **Protonated epoxide**

The acid reacts with the epoxide to produce a protonated epoxide.



Protonated epoxide **Weak nucleophile** **Protonated glycol** **Glycol**

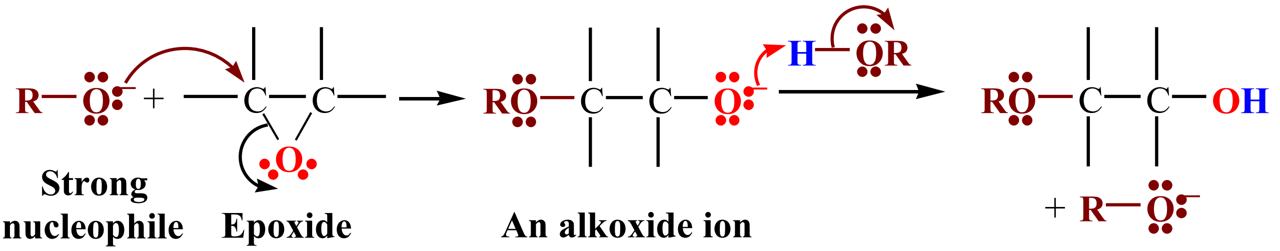
The protonated epoxide reacts with the weak nucleophile (water) to form a protonated glycol, which then transfers a proton to a molecule of water to form the glycol and a hydronium ion.

1. The highly strained three-membered ring of epoxides makes them much more reactive toward nucleophilic substitution than other ethers.
   1) Acid catalysis assists epoxide ring opening by providing a better leaving group (an alcohol) at the carbon atom undergoing nucleophilic attack.

2. Epoxides Can undergo base-catalyzed ring opening:

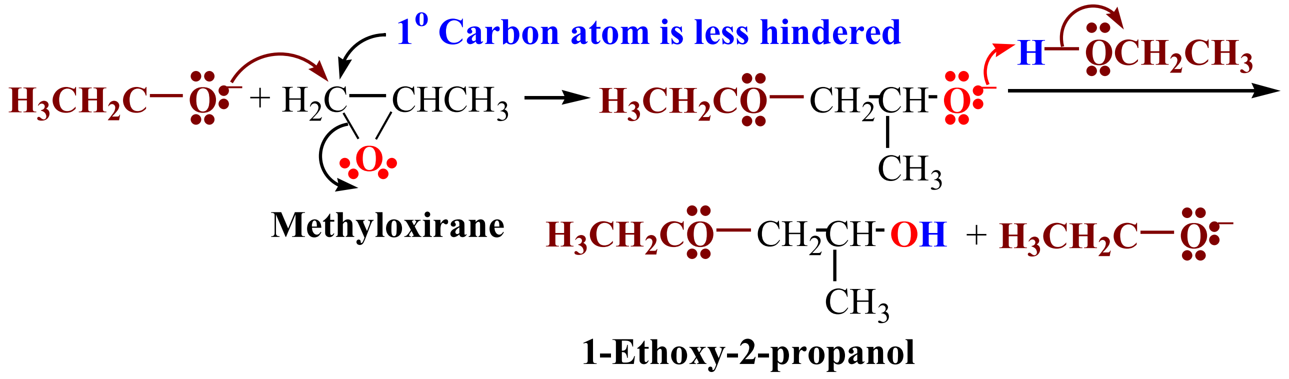
A Mechanism for the Reaction

Base-Catalyzed Ring Opening of an Epoxide

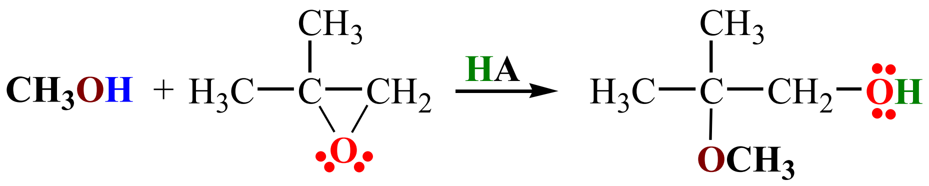


A strong nucleophile such as an alkoxide ion or a hydroxide ion is able to open the strained epoxide ring in a direct S_N2 reaction.

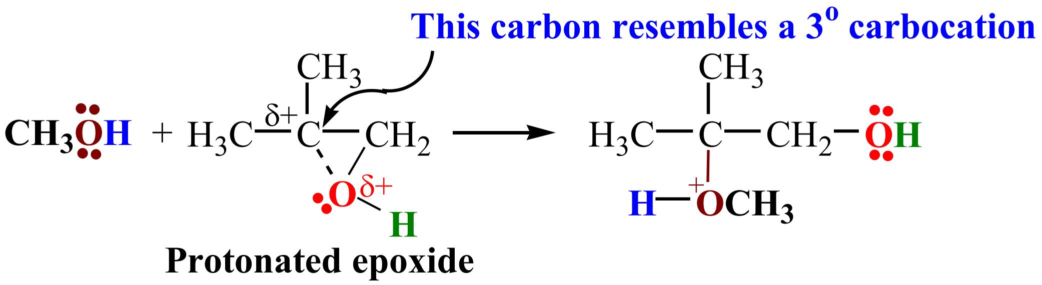
1) If the epoxide is unsymmetrical, the **nucleophile** attacks primarily at ***the less substituted carbon atom*** in **base-catalyzed ring opening**.



2) If the epoxide is unsymmetrical, the **nucleophile** attacks primarily at ***the more substituted carbon atom*** in **acid-catalyzed ring opening**.

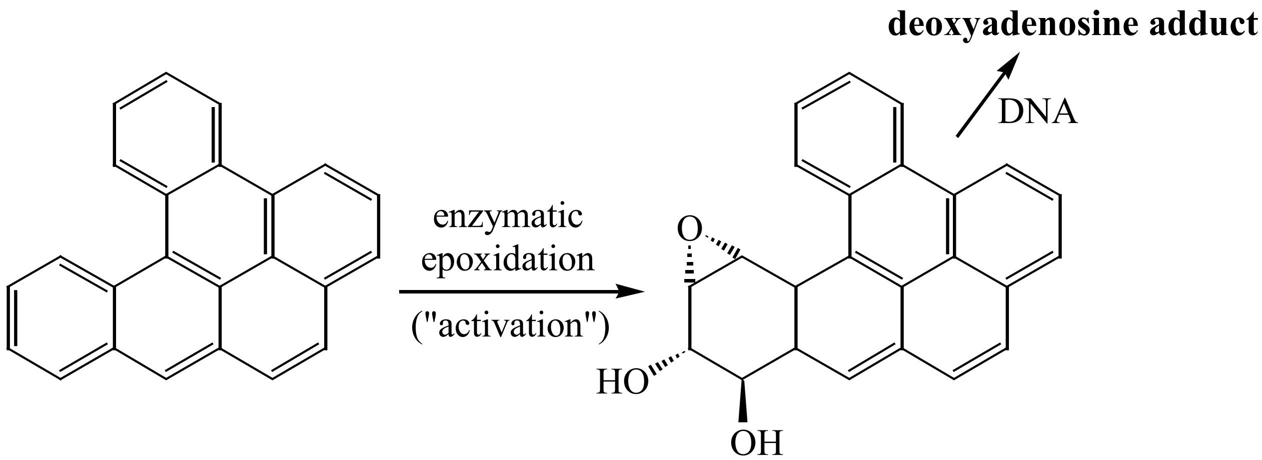


i) Bonding in the protonated epoxide is unsymmetrical, which the more highly substituted carbon atom bearing a considerable positive charge; the reaction is S_N1 like.



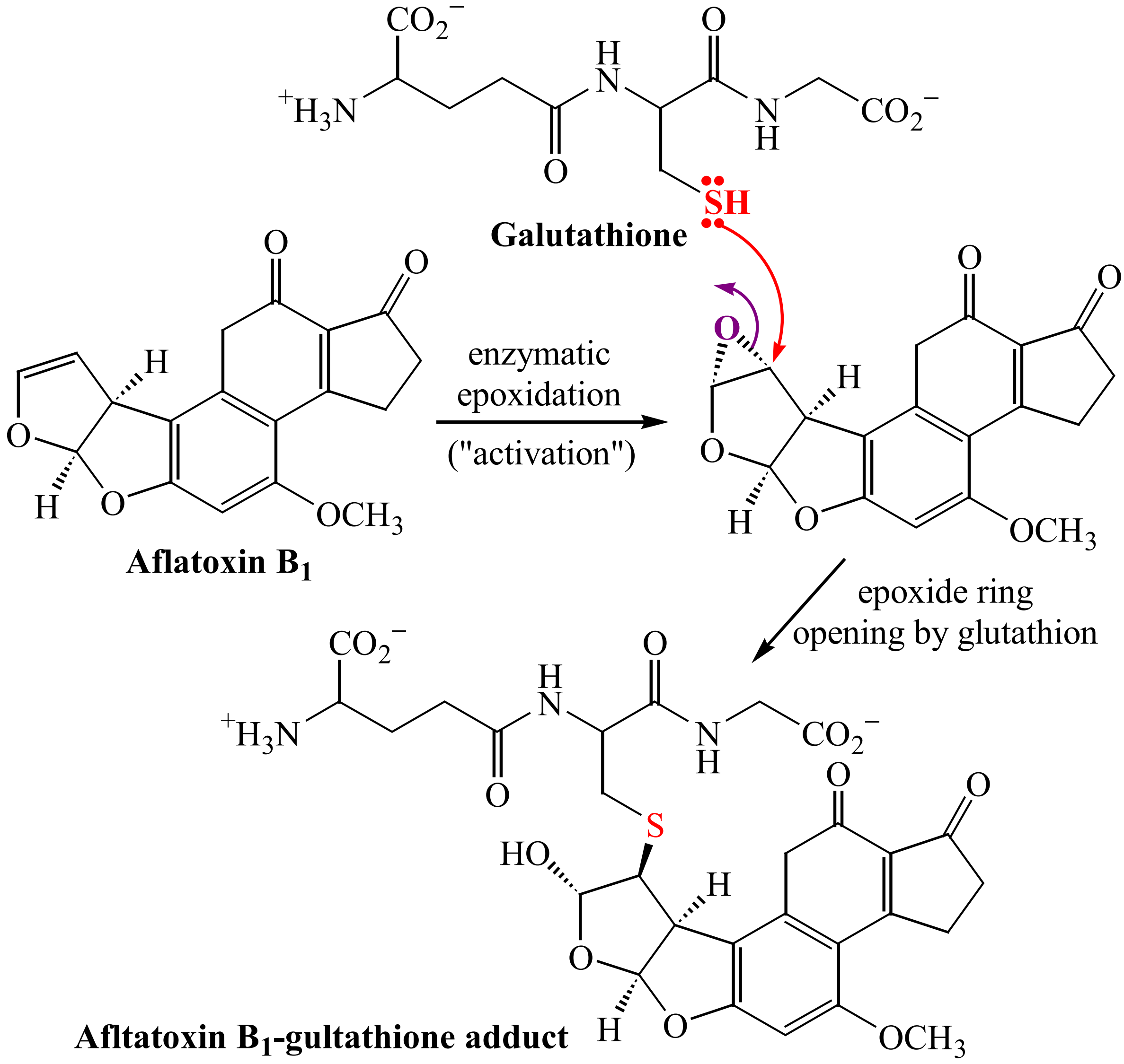
The Chemistry of Epoxides, Carcinogens, and Biological Oxidation

1. Certain molecules from the environment becomes carcinogenic by "activation" through metabolic processes that are normally involved in preparing them for excretion.
2. Two of the most carcinogenic compounds known: dibenzo[*a*,*l*]pyrene, a polycyclic aromatic hydrocarbon (PAH) and aflatoxin B_1, a fungal metabolite.
  1) During the course of oxidative processing in the liver and intestines, these molecules undergo epoxidation by enzymes called P450 cytochromes.
    i) The epoxides are exceptionally reactive nucleophiles and it is precisely because of this that they are carcinogenic.
    ii) The epoxides undergo very facile nucleophilic substitution reactions with DNA.
    iii) Nucleophilic sites on DNA react to open the epoxide ring, causing alkylation of the DNA by formation of a covalent bond with the carcinogen.
    iv) Modification of the DNA in this way causes onset of the disease state.



Dibenzo[*a,l*]pyrene **Dibenzo[*a,l*]pyrene-11,12-diol-13,14-epoxide**

2) The normal pathway toward excretion of foreign molecules like aflatoxin B_1 and dibenzo[*a,l*]pyrene, however, also involves nucleophilic substitution reactions of their epoxides.



i) One pathway involves opening of the epoxide ring by nucleophilic substitution

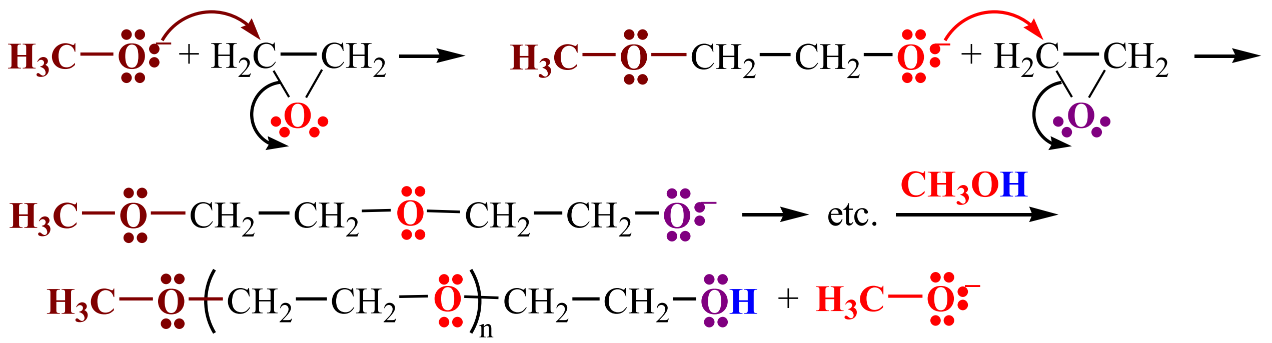
with glutathione.

ii) Glutathion is a relatively polar molecule that has a strongly nucleophilic sulfhydryl (thiol) group.

iii) The newly formed covalent derivative is readily excreted through aqueous pathways because it is substantially more polar than the original epoxide.

11.18A Polyether Formation

1. Treating ethylene oxide with sodium methoxide (in the presence of a small amount of methanol) can result in the formation of a **polyether**.



Poly(ethylene glycol)
(a polyether)

1) This an example of **anionic polymerization**.

i) The polymer chains continue to grow until methanol protonates the alkoxide group at the end of the chain.

ii) The average length of the growing chains and, therefore, the average molecular weight of the polymer can be controlled by the amount of methanol present.

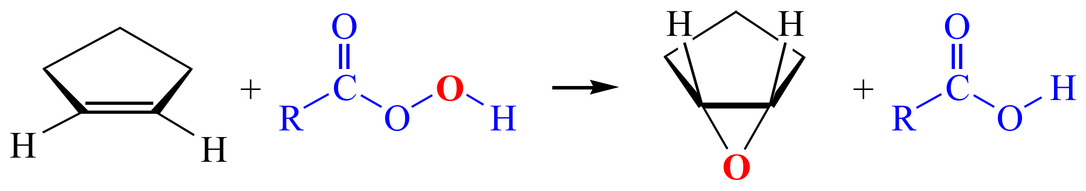
iii) The physical properties of the polymer depend on its average molecular weight.

2) Polyethers have high water solubilities because of their ability to form multiple hydrogen bonds to water molecules.

i) Marketed commercially as **carbowaxes**, these polymers have a variety of uses, ranging from use in gas chromatography columns to applications in cosmetics.

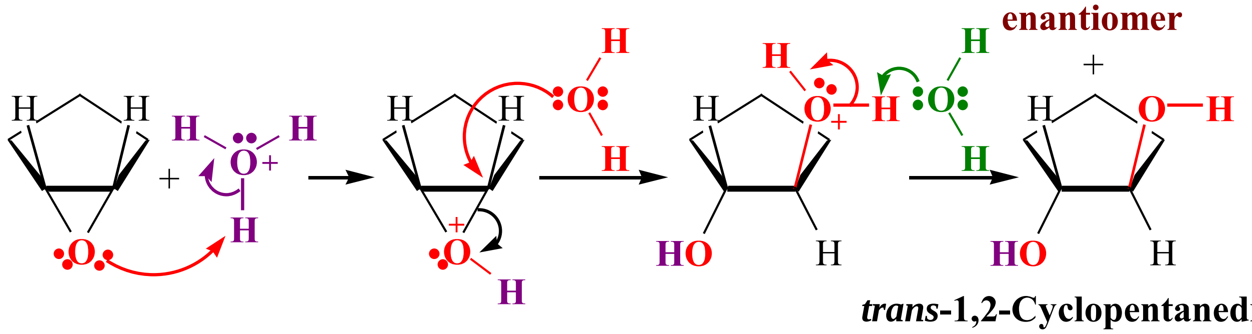
11.19 ANTI HYDROXYLATION OF ALKENES VIA EPOXIDES

1. Epoxidation of cyclopentene produces 1,2-epoxycyclopentane:



Cyclopentene **1,2-Epoxycyclopentane**

2. Acid-catalyzed hydrolysis of 1,2-epoxycyclopentane yields a *trans*-diol, *trans*-1,2-cyclopentanediol.



***trans*-1,2-Cyclopentanediol**

1) Water acting as a nucleophile attacks the protonated epoxide from the side opposite the epoxide group.
2) The carbon atom being attacked undergoes an inversion of configuration.
3) Attack at the other carbon atom produces the enantiomeric form of *trans*-1,2-cyclopentanediol.

3. Epoxidation followed by acid-catalyzed hydrolysis constitutes a method for **anti hydroxylation** of a double bond.

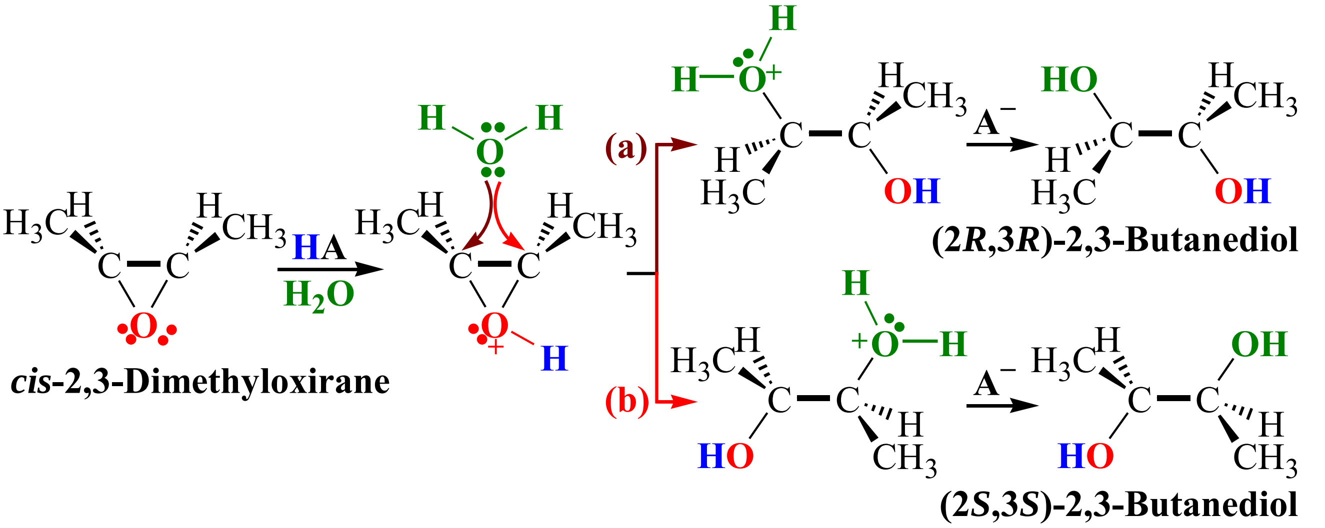


Figure 11.2 Acid-catalyzed hydrolysis of *cis*-2,3-dimethyloxirane yields (2*R*,3*R*)-2,3-butanediol by path (a) and (2*S*,3*S*)-2,3-butanediol by path (b).

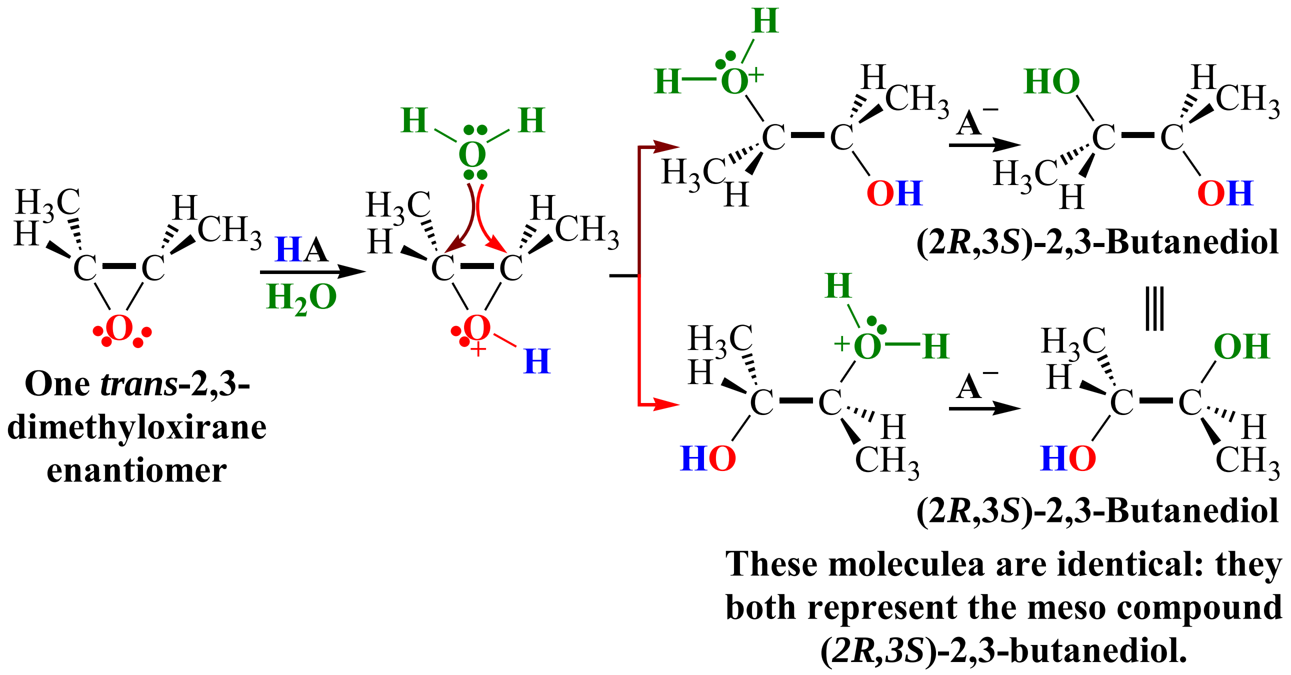
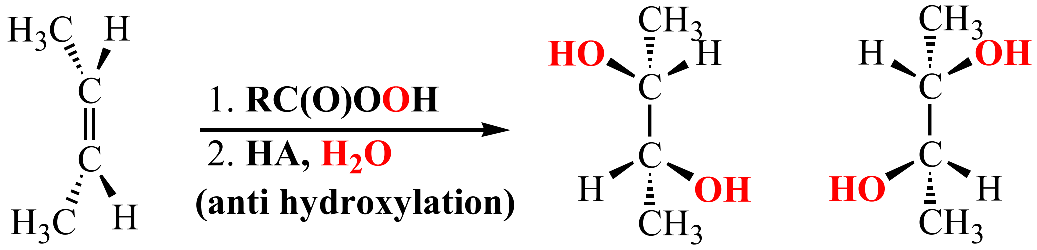
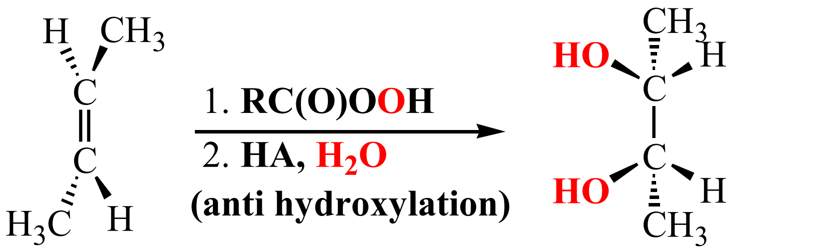


Figure 11.3 The acid-catalyzed hydrolysis of one *trans*-2,3-dimethyloxirane enantiomer produces the meso (2*R*,3*S*)-2,3-butanediol by path (a) or path (b). Hydrolysis of the other enantiomer (or the racemic modification) would yield the same product.



cis-2-Butene (*R*,*R*) (*S*,*S*)

Enantiomeric 2,3-butanediols



trans-2-Butene *meso*-2,3-Butanediols

Figure 11.4 The overall result of epoxidation followed by acid-catalyzed hydrolysis is a stereospecific anti hydroxylation of the double bond. *cis*-2-Butene yields the enantiomeric 2,3-butanediols; *trans*-2-butene yields the meso compound.

11.20 Crown Ethers: Nucleophilic Substitution Reactions in Relatively Nonpolar Aprotic Solvents by Phase-Transfer Catalysis

1. S_N2 reactions take place much more rapidly in polar aprotic solvents.
   1) **In polar aprotic solvents the nucleophile is only very slightly solvated and is, consequently, highly reactive**.
   2) This increased reactivity of nucleophile is a distinct advantage ⇒ Reactions that might have taken many hours or days are often over in a matter of minutes.
   3) There are certain disadvantages that accompany the use of solvents such as DMSO and DMF.
      i) These solvents have very high boiling points, and as a result they are often difficult to remove after the reaction is over.
      ii) Purification of these solvents is time consuming, and they are expensive.
      iii) At high temperatures certain of these polar aprotic solvents decompose.

2. In some ways the ideal solvent for an S_N2 reaction would be a ***nonpolar*** aprotic solvent such as a hydrocarbon or a relatively nonpolar chlorinated hydrocarbon.

1) They have low boiling points, they are inexpensive, and they are relatively stable.

2) Hydrocarbon or chlorinated hydrocarbon were seldom used for nucleophilic substitution reactions because of their inability to dissolve ionic compounds.

3. **Phase-transfer catalysts** are used with two immiscible phases in contact —— often an aqueous phase containing an ionic reactant and an organic (benzene, $CHCl_3$, etc.) containing the organic substrate.

1) Normally the reaction of two substances in separate phases like this is inhibited because of the inability of the reagents to come together.

2) Adding a phase-transfer catalyst solves this problem by transferring the ionic reactant into the organic phase.

i) Because the reaction medium is aprotic, an S_N2 reaction occurs rapidly.

4. **Phase-transfer catalysis**:

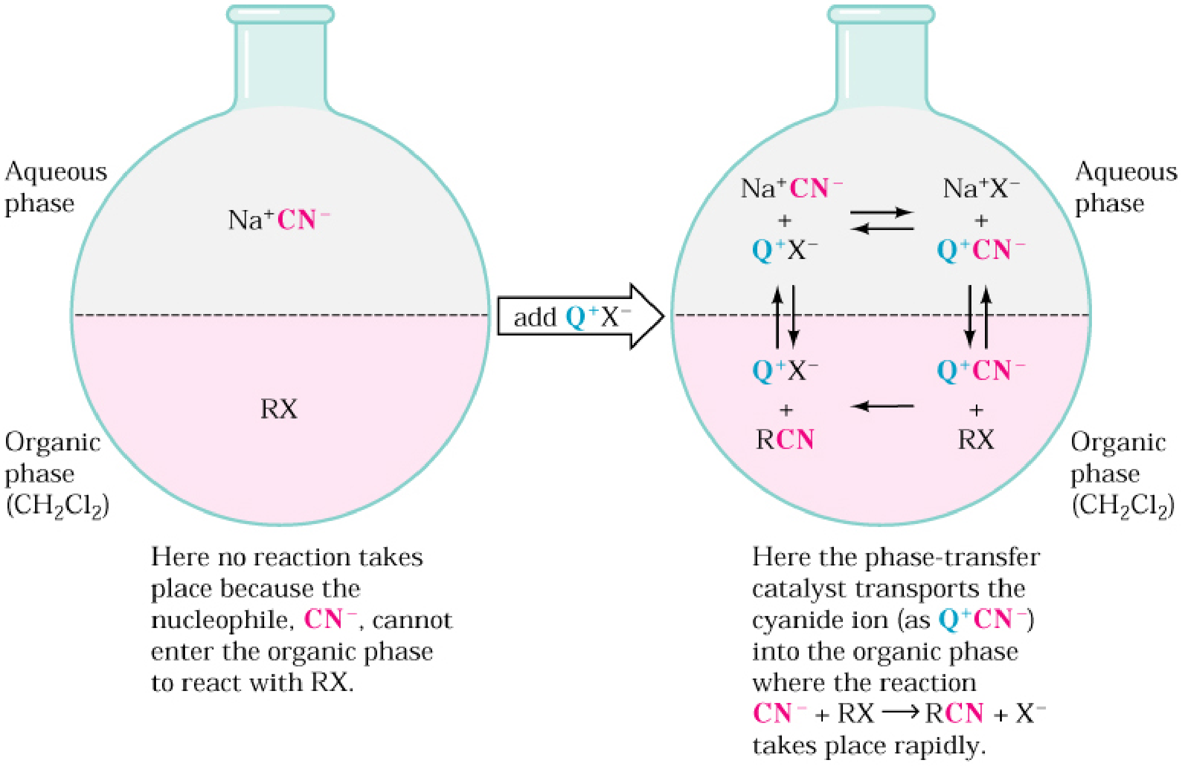


Figure 11.5 Phase-transfer catalysis of the S_N2 reaction between sodium cyanide and an alkyl halide.

1) The phase-transfer catalyst (**Q^+X^-**) is usually a quaternary ammonium halide (**$R_4N^+X^-$**) such as tetrabutylammonium halide **$(CH_3CH_2CH_2CH_2)_4N^+X^-$**.

2) The phase-transfer catalyst causes the transfer of the nucleophile (e.g. CN^-) as an ion pair [**Q^+CN^-**] into the organic phase.

3) This transfer takes place because the cation (**Q^+**) of the ion pair, with its four alkyl groups, resembles a hydrocarbon in spite of its positive charge.

i) It is said to be **lipophilic** — it prefers a nonpolar environment to an aqueous one.

4) In the organic phase the nucleophile of the ion pair (**CN^-**) reacts with the organic substrate **RX**.

5) The cation (**Q^+**) [and anion (**X^-**)] then migrate back into the aqueous phase to complete the cycle.

i) This process continues until all of the nucleophile or the organic substrate has reacted.

5. An example of **phase-transfer catalysis**:

1) The nucleophilic substitution reaction of 1-chlorooctane (in decane) and sodium cyanide (in water):

$$\mathbf{CH_3(CH_2)_6CH_2Cl}\text{ (in decane)} \xrightarrow[\text{aqueous } \mathbf{NaCN}\text{, 105 °C}]{\mathbf{R_4N^+Br^-}} \mathbf{CH_3(CH_2)_6CH_2CN}$$

i) The reaction (at 105 °C) is complete in less than 2 h and gives a 95% yield of the substitution product.

6. Many other types of reactions than nucleophilic substitution are also amenable to **phase-transfer catalysis**.

1) Oxidation of alkenes dissolved in benzene can be accomplished in excellent yield using potassium permanganate (in water) when a quaternary ammonium salt is present.

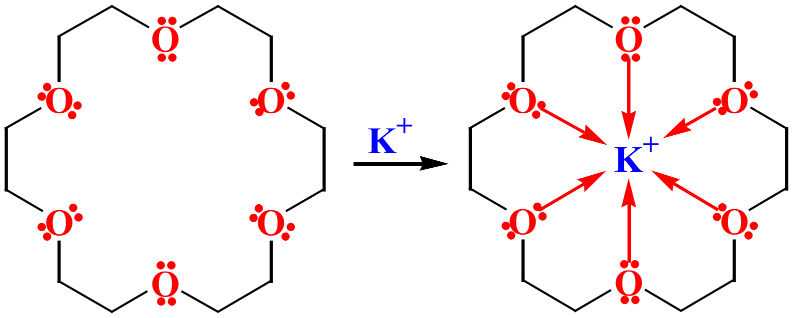
$$CH_3(CH_2)_5CH{=}CH_2 \text{ (in benzene)} \xrightarrow[\text{aqueous } KMnO_4,\ 35\ ^{o}C]{R_4N^+Br^-} CH_3(CH_2)_5CO_2H + HCO_2H \ \mathbf{(99\%)}$$

i) Potassium permanganate can be transferred to benzene by quaternary ammonium salts to give "purple benzene" which can be used as a test reagent for unsaturated compounds ⇒ the **purple** color of **$KMnO_4$** disappears and the solution becomes **brown** (**MnO_2**).

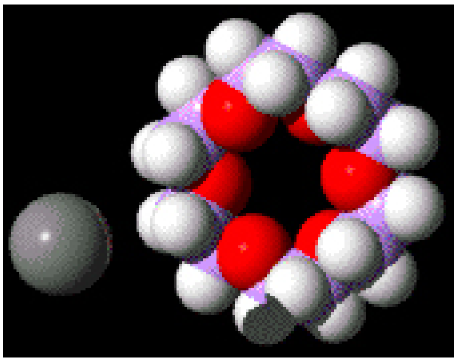
11.20A Crown Ethers

1. **Crown ethers** are also phase-transfer catalysts and are able to transport ionic compounds into an organic phase.

1) **Crown ethers** are cyclic polymers of ethylene glycol such as 18-crown-6:



18-Crown-6



2) Crown ethers are named as *x*-crown-*y* where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms.

3) The relationship between crown ether and the ion that is transport is called a **host-guest relationship**.

i) The crown ether acts as the **host**, and the coordinated cation is the **guest**.

2. The Nobel Prize for Chemistry in 1987 was awarded to Charles J. Pedersen (retired from DuPont company), Donald J. Cram (retired from the University of California, Los Angeles), and Jean-Marie Lehn (Louis Pasteur University, Strasbourg, France) for their development of crown ethers and other molecules "with structure specific interactions of high selectivity".

1) Their contributions to our understanding of what is now called "**molecular**

recognition" have implications for how enzymes recognize their substrates, how hormones cause their effects, how antibodies recognize antigens, how neurotransmitters propagate their signals, and many other aspects of biochemistry.

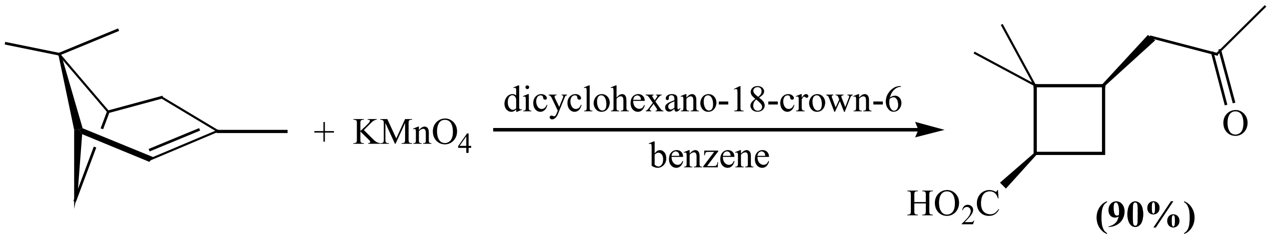
3. When crown ethers coordinate with a metal cation, they thereby convert the metal ion into a species with a hydrocarbonlike exterior.
   1) The 18-crown-6 coordinates very effectively with potassium ions because the cavity size is correct and because the six oxygen atoms are ideally situated to donate their electron pairs to the central ion.

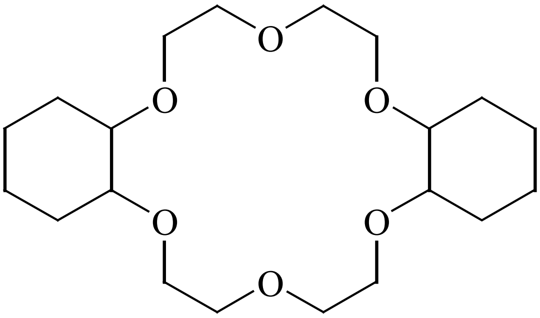
4. Crown ethers render many salts soluble in nonpolar solvents.
   1) Salts such as KF, KCN, and CH_3CO_2K can be transferred into aprotic solvents by using catalytic amounts of 18-crown-6.
   2) In the organic phase the relatively unsolvated anions of these salts can carry out a nucleophilic substitution reaction on an organic substrate.

$$\mathbf{RCH_2X + K^+CN^-} \xrightarrow[\text{benzene}]{\text{18-crown-6}} \mathbf{RCH_2CN + K^+X^-}$$

$$\mathbf{C_6H_5CH_2Cl + K^+F^-} \xrightarrow[\text{benzene}]{\text{18-crown-6}} \mathbf{C_6H_5CH_2F + K^+Cl^-}$$

(100%)

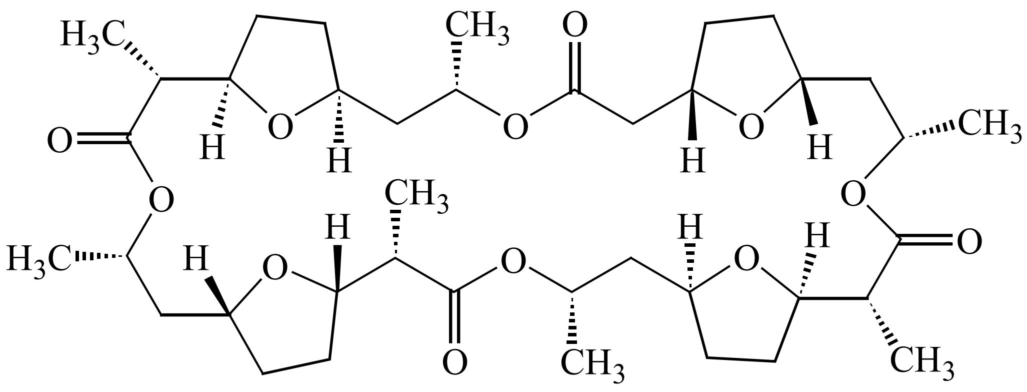




Dicyclohexano-18-crown-6

11.20B TRANSPORT ANTIBIOTICS AND CROWN ETHERS

1. There are several antibiotics called ionophores, most notably ***nonactin*** and ***valinomycin***, that coordinate with metal cations in a manner similar to that of crown ether.
2. Normally, cells must maintain a gradient between the concentrations of sodium and potassium ions inside and outside the cell wall.
   1) Potassium ions are "pumped" in; sodium ions are pumped out.
   2) The cell membrane, in its interior, is like a hydrocarbon, because it consists in this region primarily of the hydrocarbon portions of lipids.
   3) The transport of hydrated sodium and potassium ions through the cell membrane is slow, and this transport requires an expenditure of energy by the cell.
3. Nonactin upsets the concentration gradient of these ions by coordinating more strongly with potassium ions than with sodium ions.
   1) Because the potassium ions are bound in the interior of the nonactin, this host-guest complex becomes hydrocarbonlike on its surface and passes readily through the interior of the membrane.
   2) The cell membrane thereby becomes permeable to potassium ions, and the essential concentration gradient is destroyed.



Nonactin

11.21 Summary of Reactions of Alkenes, Alcohols, and Ethers

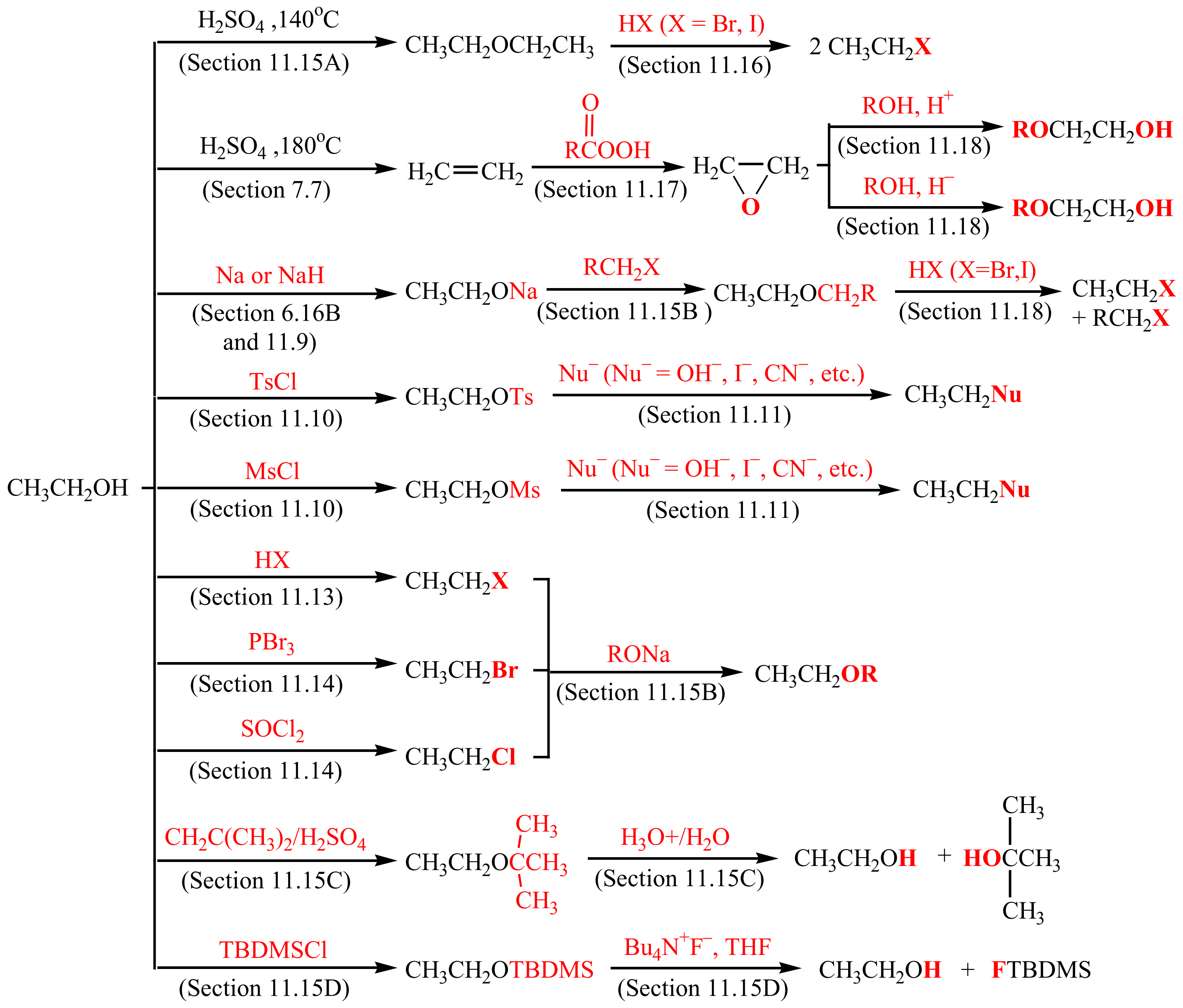


Figure 11.6 **Summary of importrant reactions of alcohols and ethers starting with ethanol.**

11.21A Alkenes in Synthesis

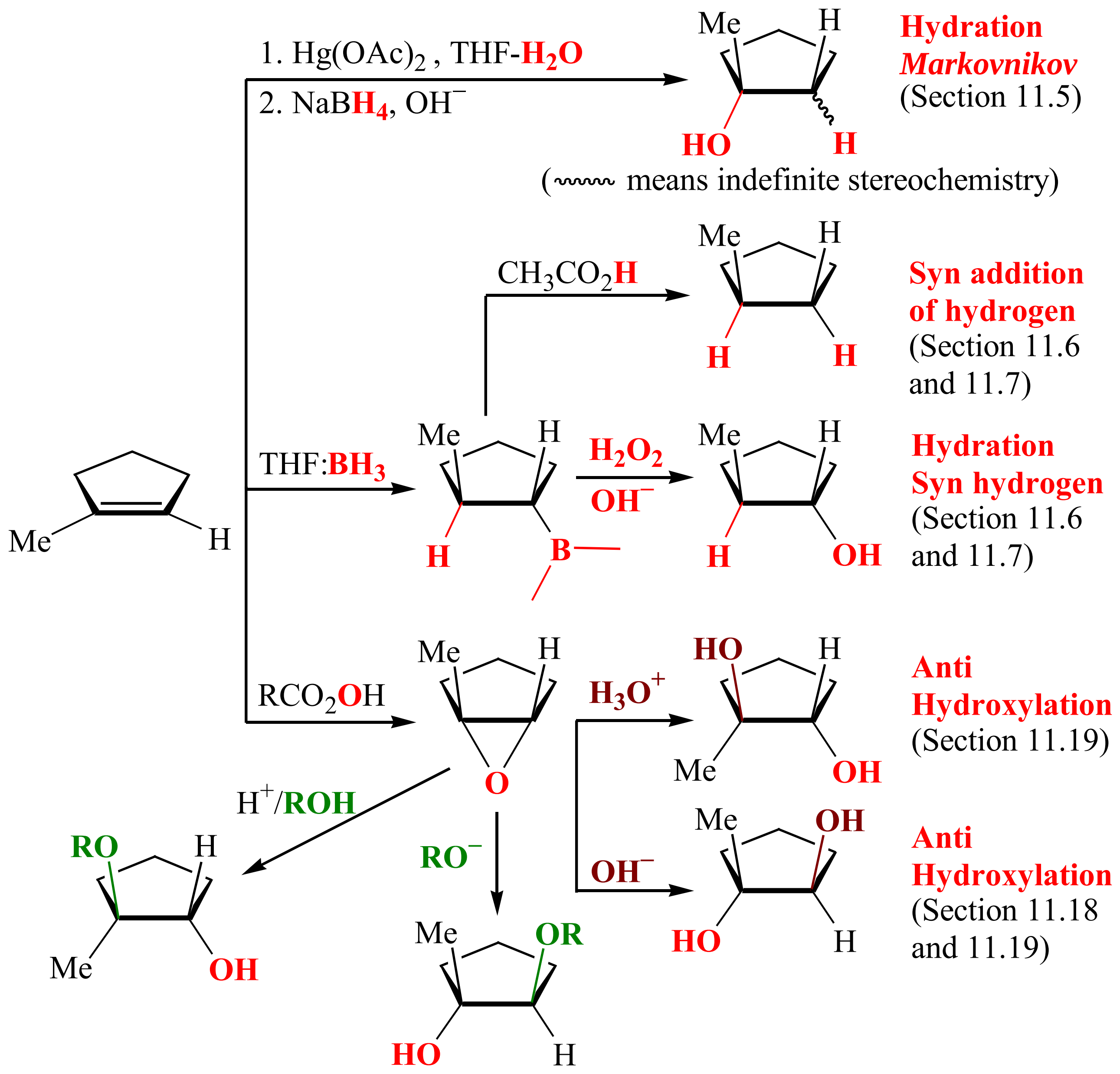


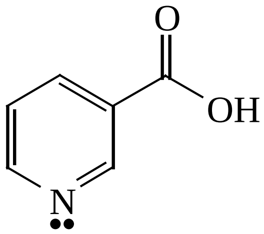
Figure 11.7 Summary of importrant reactions of alcohols and ethers starting with ethanol.

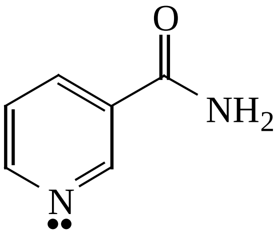
ALCOHOLS FROM CARBONYL COMPOUNDS. OXIDATION-REDUCTION AND ORGANOMETALLIC COMPOUNDS

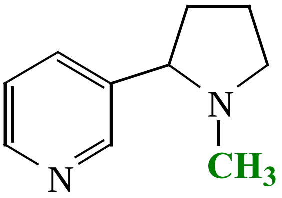
THE TWO ASPECTS OF THE COENZYME NADH

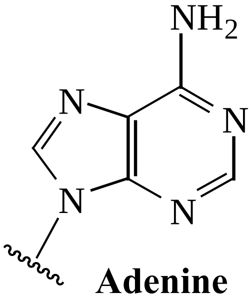
1. The role of many of the vitamins in our diet is to become coenzymes for enzymatic reactions.
   1) Coenzymes are molecules that are part of the organic machinery used by some enzymes to catalyze reactions.

2. The vitamins niacin (nicotinic acid, 菸鹼酸) and its amide niacin amide are precursors to the coenzyme nicotinamide adenine dinucleotide.

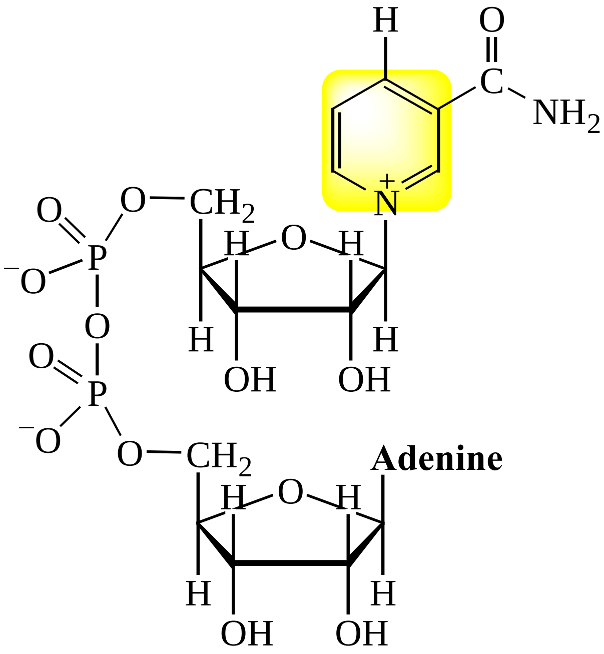




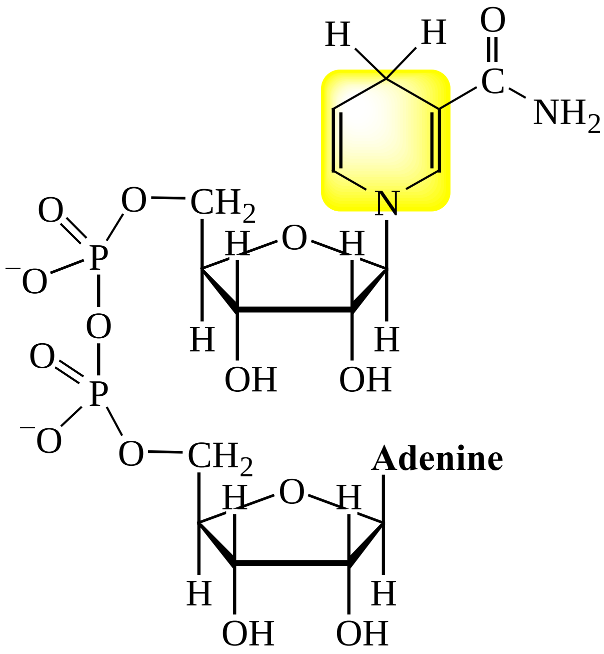




Niacin (Nicotinic acid) **Nicotinamide** **Nicotine** **Adenine**

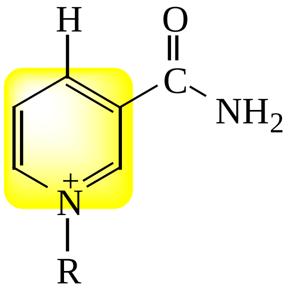


nicotinamide adenine dinucleotide



reduced nicotinamide adenine dinucleotide

NAD$^+$ **NADH**



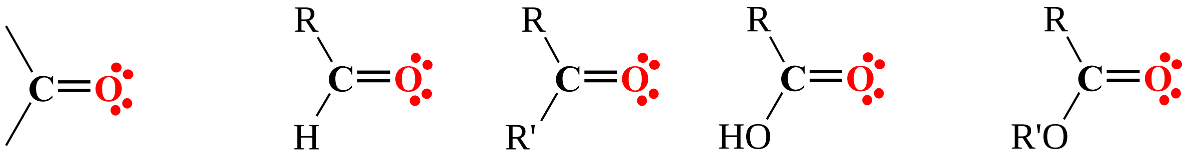
NAD$^+$

1) Soybeans are one dietary source of niacin.

3. **NAD$^+$** is the oxidized form while **NADH** is the reduced form of the coenzyme.
   1) **NAD$^+$** serves as an oxidizing agent.
   2) **NADH** is a reducing agent that acts as an electron donor and frequently as a biochemical source of hydride (“**H**$^-$”).

12.1 INTRODUCTION

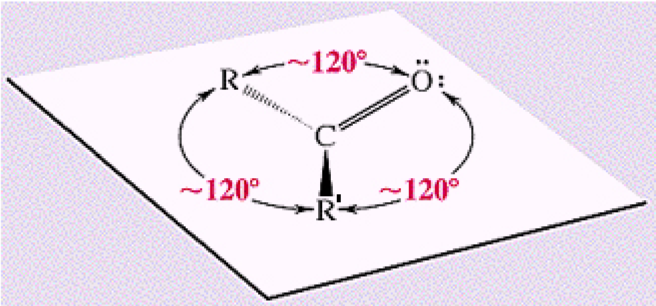
1. Carbonyl compounds include aldehydes, ketones, carboxylic acids, and esters.



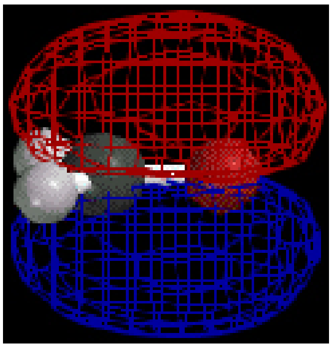
The carbonyl group **An aldehyde** **A ketone** **A carboxylic** **A carboxylate ester**

12.1A STRUCTURE OF THE CARBONYL

1. The carbonyl carbon atom is sp^2 hybridized ⇒ it and the three groups attached to it lie in the same plane.
   1) A trigonal plannar structure ⇒ the bond angles between the three attached atoms are approximately 120°.

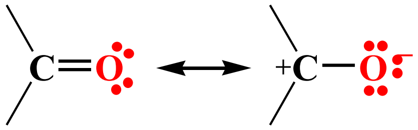


2. The carbon-oxygen double bond consists of two electrons in a σ bond and two electrons in a π bond.
   1) The π bond is formed by overlap of the carbon *p* orbital with a *p* orbital from the oxygen atom.
   2) The electron pair in the π bond occupies both lobes (above and below the plane of the σ bonds).

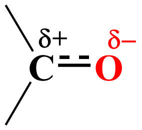


The π bonding molecular orbital of formaldehyde (HCHO). The electron pair of the π bond occupies both lobes.

3. The more electronegative oxygen atom strongly attracts the electrons of both the σ bond and the π bond, causing the carbonyl group to be highly polarized ⇒ the carbon atom bears a substantial positive charge and the oxygen bears a substantial negative charge.
   1) Resonance structures for the carbonyl group:

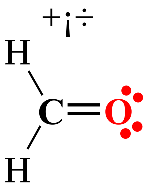


or

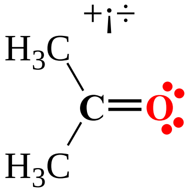


Resonance structure for the carbonyl group **Hybrid**

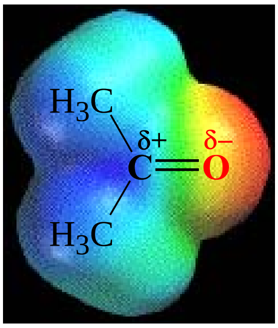
   2) Carbonyl compounds have rather large dipole moments as a result of the polarity of the carbon-oxygen bond.



Formaldehyde
μ = 2.27 D



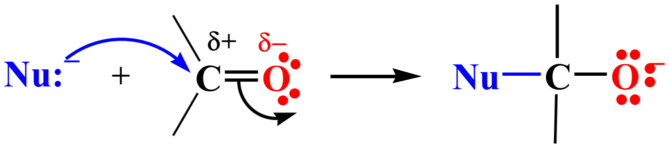
Acetone
μ = 2.88 D



An electrostatic potential map for acetone

12.1B Reaction of Carbonyl Compounds with Nucleophiles

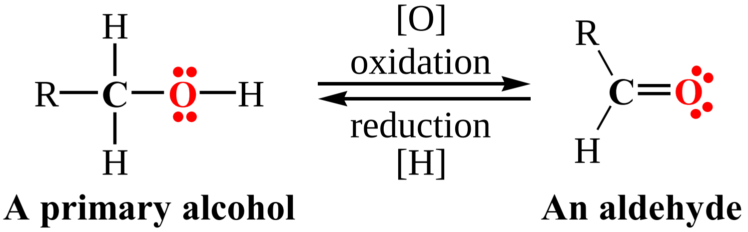
1. One of the most important reactions of carbonyl compounds is the **nucleophilic addition** to the carbonyl group.
   1) The carbonyl carbon bears a partial positive charge ⇒ the carbonyl group is susceptible to nucleophilic attack.
   2) The electron pair of the nucleophile forms a bond to the carbonyl carbon atom.
   3) The carbonyl carbon can accept this electron pair because one pair of electrons of the carbon-oxygen group double bond can shift out to the oxygen.



2. The carbon atom undergoes a change in its geometry and its hybridization state during the reaction.
   1) It goes from a trigonal planar geometry and sp^2 hybridization to a tetrahedral geometry and sp^3 hybridization.
   2) The electron pair of the nucleophile forms a bond to the carbonyl carbon atom.

3. Two important nucleophiles that add to carbonyl compounds:
   1) **Hydride ions** form compounds such as $NaBH_4$ or $LiAlH_4$.
   2) **Carbanions** form compounds such as RLi or RMgX.

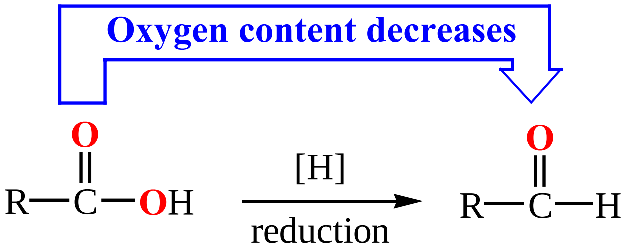
4. Oxidation of alcohols and reduction of carbonyl compounds:



12.2 Oxidation-Reduction Reactions in Organic Chemistry

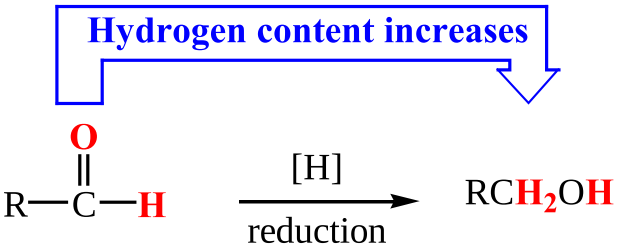
1. ***Reduction of an organic molecule usually corresponds to increasing its hydrogen content or to decreasing its oxygen content.***

   1) Converting a carboxylic acid to an aldehyde is a **reduction**:

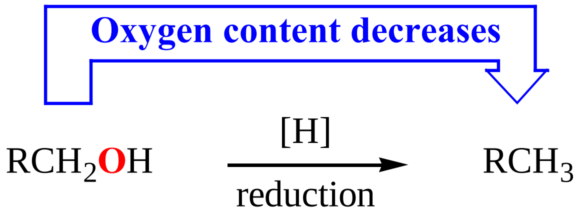


[H] stands for a reduction of the compound

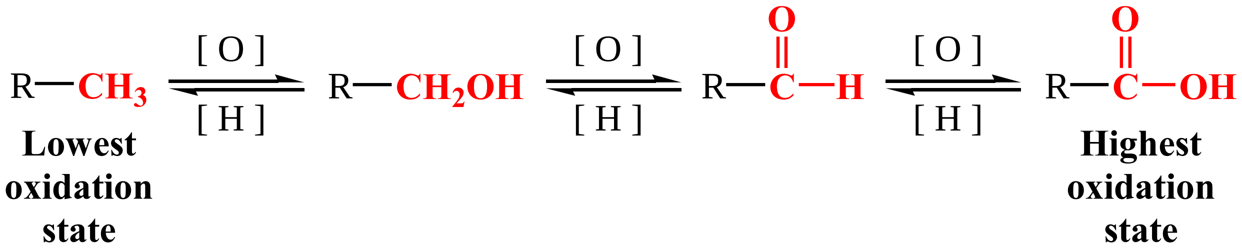
   2) Converting an aldehyde to an alcohol is a **reduction**:



   3) Converting a n alcohol to an alkane is a **reduction**:

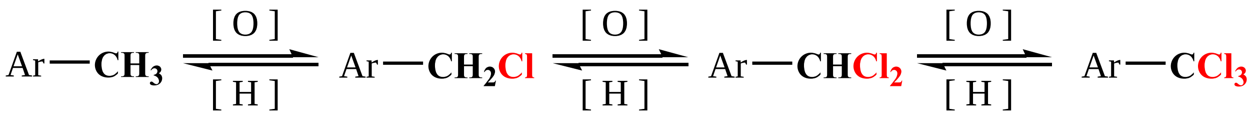


2. ***Oxidation of an organic molecule usually corresponds to increasing its oxygen content or to decreasing its hydrogen content.***



[O] stands for an oxidation of the compound

1) ***Oxidation of an organic compound may be more broadly defined as a reaction that increases its content of any element more electronegative than carbon.***

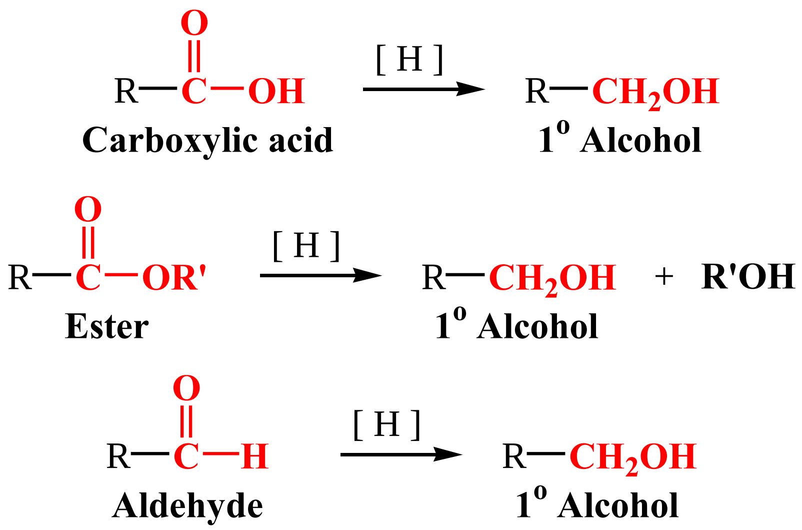


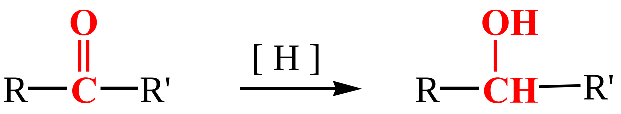
3. When an organic compound is reduced **the reducing agent** must be oxidized. When an organic compound is oxidized **the oxidizing agent** must be reduced.

1) The **oxidizing** and **reducing agents** are often inorganic compounds.

12.3 ALCOHOLS BY REDUCTION OF CARBONYL COMPOUNDS

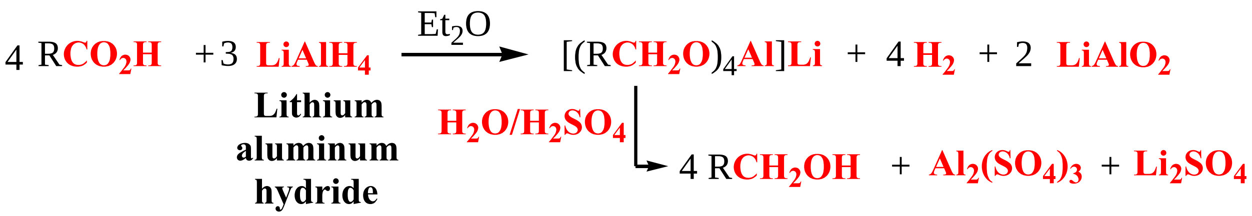
1. Primary and secondary alcohols can be synthesized by the reduction of a variety of compounds that contain the carbonyl group.

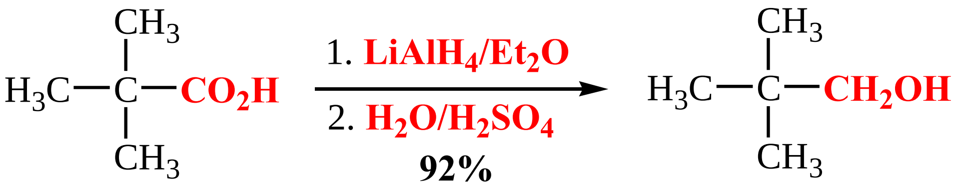




Ketone **2^o Alcohol**

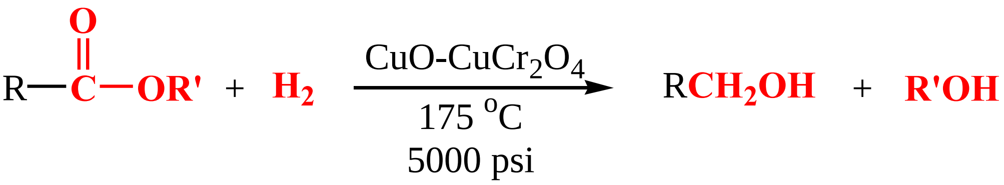
2. Reduction of carboxylic acids are the most difficult, but they can be accomplished with the powerful reducing agent **lithium aluminum hydride** ($LiAlH_4$, abbreviated LAH).

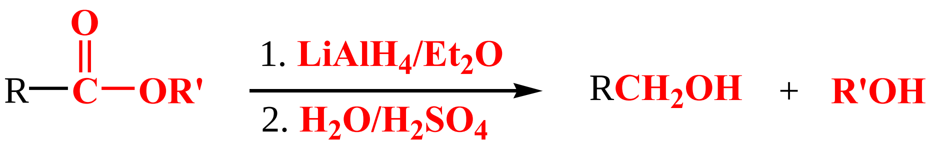




2,2-Dimethylpropanoic acid **Neopentyl alcohol**

3. Esters can be reduced by high-pressure hydrogenation (a reaction preferred for industrial processes and often referred to as "**hydrogenolysis**" because the C–O bond is cleaved in the process), or through the use of $LiAlH_4$.

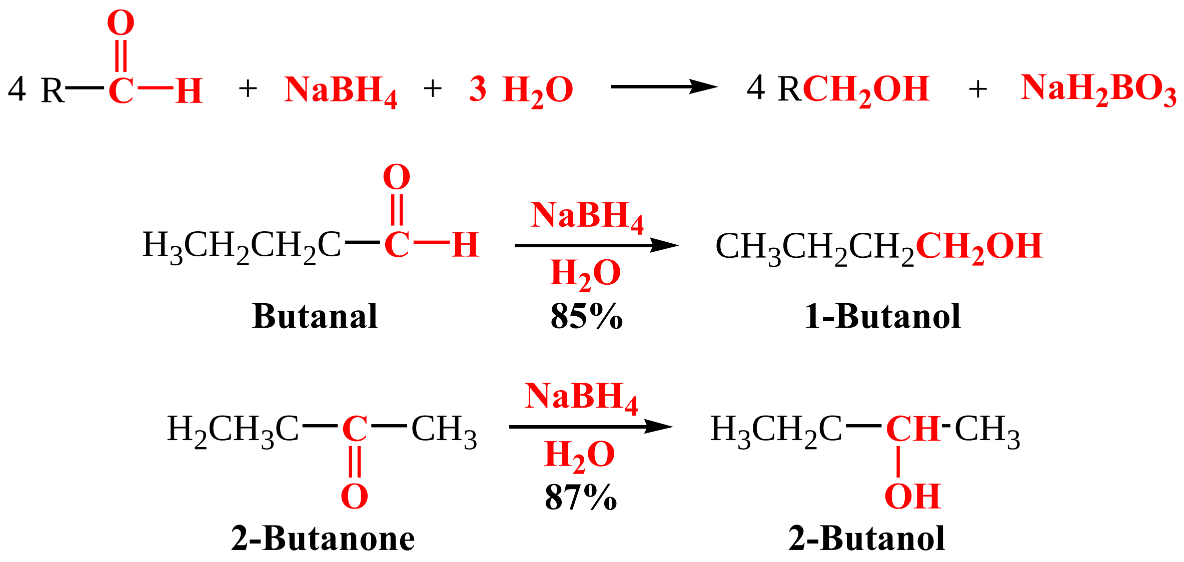




1) The latter method is the one most commonly used now in small-scale laboratory syntheses.

4. Aldehydes and ketones can be reduced to alcohols by hydrogenation, or sodium in alcohol, and by the use of $LiAlH_4$.

1) The most often used reducing agent is sodium borohydride ($NaBH_4$).

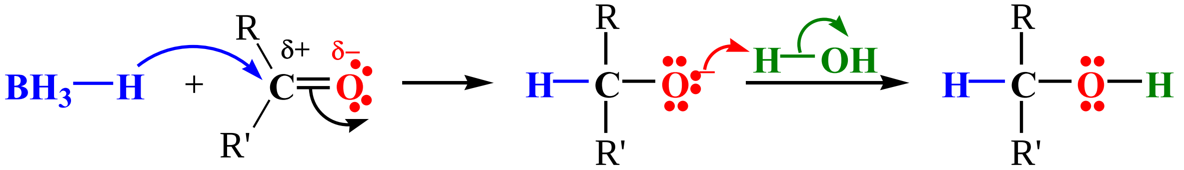


5. The key step in the reduction of a carbonyl compound by either $LiAlH_4$ or $NaBH_4$ is the transfer of a **hydride ion** from the metal to the carbonyl carbon.

1) The hydride ion acts as a ***nucleophile***.

A Mechanism for the Reaction

Reduction of Aldehydes and Ketones by Hydride Transfer

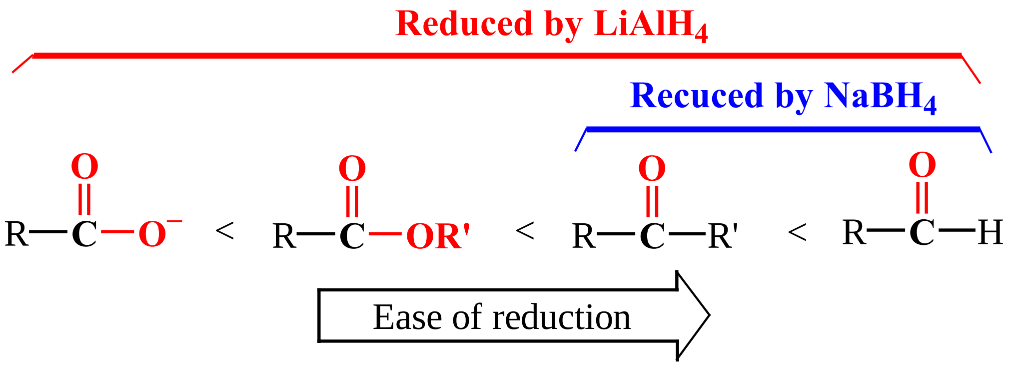


Hydride transfer **Alkoxide ion** **Alcohol**

6. $NaBH_4$ is a less powerful reducing agent than $LiAlH_4$.

1) $LiAlH_4$ reduces acids, esters, aldehydes, and ketones.

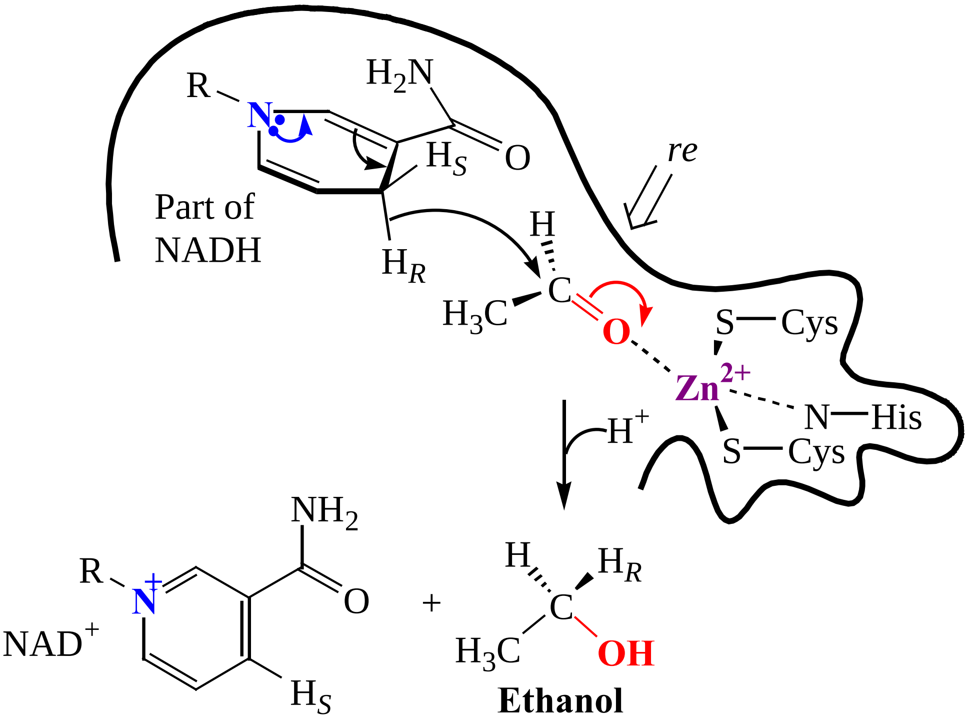
2) $NaBH_4$ reduces only aldehydes and ketones.



7. **LiAlH$_4$ reacts violently with water** $\Rightarrow$ reductions with LiAlH$_4$ must be carried out in anhydrous solutions, usually in anhydrous ether.
   1) Ethyl acetate is added cautiously after the reaction is over to decompose excess LiAlH$_4$, then water is added to decompose the aluminum complex.
   2) NaBH$_4$ reductions can be carried out in water or alcohol solutions.

The Chemistry of Alcohol Dehydrogenase

1. When the enzyme **alcohol dehydrogenase** converts acetaldehyde to ethanol, **NADH** acts as a reducing agent by transferring a hydride from C4 of the nicotinamide ring to the carbonyl group of acetaldehyde.
   1) The nitrogen of the nicotinamide ring facilitates this process by contributing its nonbonding electron pair to the ring, which together with loss of the hydride converts the ring to the energetically more stable ring found in **NAD$^+$**.
   2) The ethoxide anion resulting from hydride transfer to acetaldehyde is then protonated by the enzyme to form ethanol.



2. Although the carbonyl group of acetaldehyde that accepts the hydride is inherently electrophilic, the enzyme enhances this property by providing a zinc ion as a Lewis acid to coordinate with the carbonyl oxygen.
   1) The Lewis acid stabilizes the negative charge that develops on the oxygen in the transition state.
   2) The role of the enzyme's protein scaffold is to hold the zinc ion, coenzyme, and substrate in the three-dimensional array required to lower the energy of the transition state.
   3) The reaction is reversible and when the relative concentration of ethanol is high, alcohol dehydrogenase carries out the oxidation of ethanol ⇒ alcohol dehydrogenase is important in detoxication.

The Chemistry of Stereoselective Reductions of Carbonyl Groups

1. **Enantioselectivity:**
   1) Depending on the structure about the carbonyl group that is being reduced, the tetrahedral carbon that is formed by transfer of a hydride could be a new stereocenter.

i) Achiral reagents like $NaBH_4$ and $LiAlH_4$, react with equal rates at either face of an achiral trigonal planar substrate, leading to a racemic form of the product.

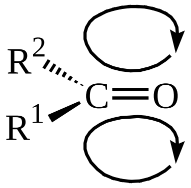
ii) Reactions involving a chiral reactant typically lead to a predominance of one ***enantiomeric form*** of a chiral product ⇒ an ***enantioselective*** reaction.

2) When enzymes like alcohol dehydrogenase, are **chiral**, reduce carbonyl groups using coenzyme NADH, they discriminate between the two faces of the trigonal planar carbonyl substrate, such that a predominance of one of the two possible stereoisomeric forms of the tetrahedral product results.

i) If the original reactant was chiral, the formation of the new stereocenter may result in preferential formation of one ***diastereomer*** of the product ⇒ a ***diastereoselectiv*** reaction.

3. ***Re*** and ***si*** **face** of a **trigonal planar center:**

1) *Re* is clockwise, *si* is counterclockwise.



re face (when looking at this face there is a clockwise sequence of priorities)

si face (when looking at this face there is a counterclockwise sequence of priorities

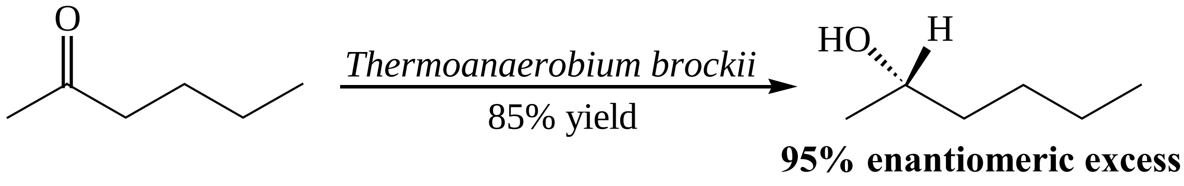
The *re* and *si* faces of a carbonyl group
(Where O > R^1 > R^2 in terms of Cahn-Inglod-Prelog priorities)

4. The preference of many NADH-dependent enzymes for either *re* or *si* face of their respective substrates is known ⇒ some of these enzymes become exceptionally useful stereoselective reagents for synthesis.

1) Yeast alcohol dehydrogenase is one of the most widely used enzymes.

2) **Extremozymes**, enzymes from thermophilic bacteria, have become important in synthetic chemistry.

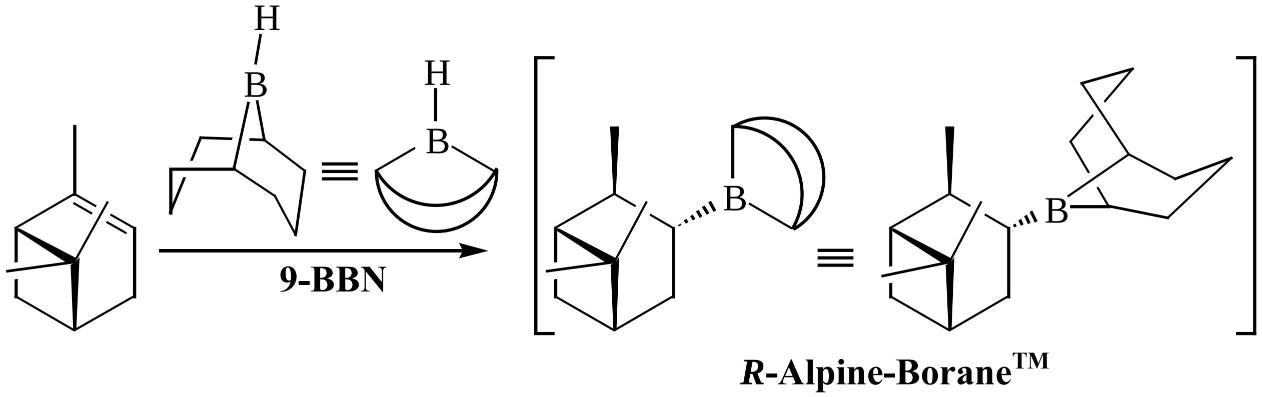
i) Use of heat-stable enzymes allows reactions to be completed faster due to the rate-enhancing factor of elevated temperature (over 100 °C in some cases), although greater enantioselectivity is achieved at lower temperature.

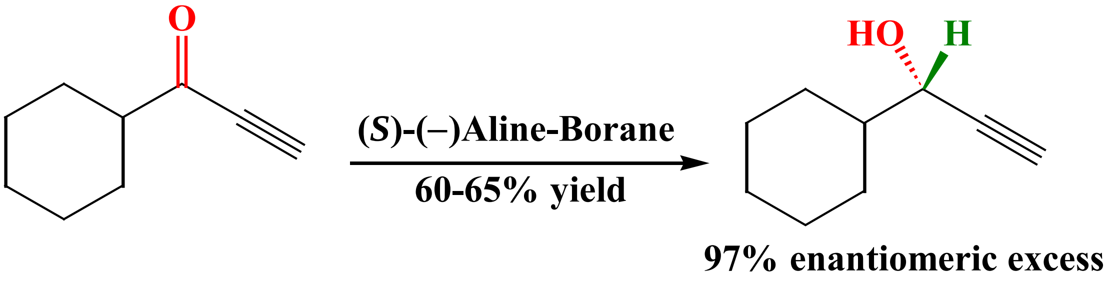


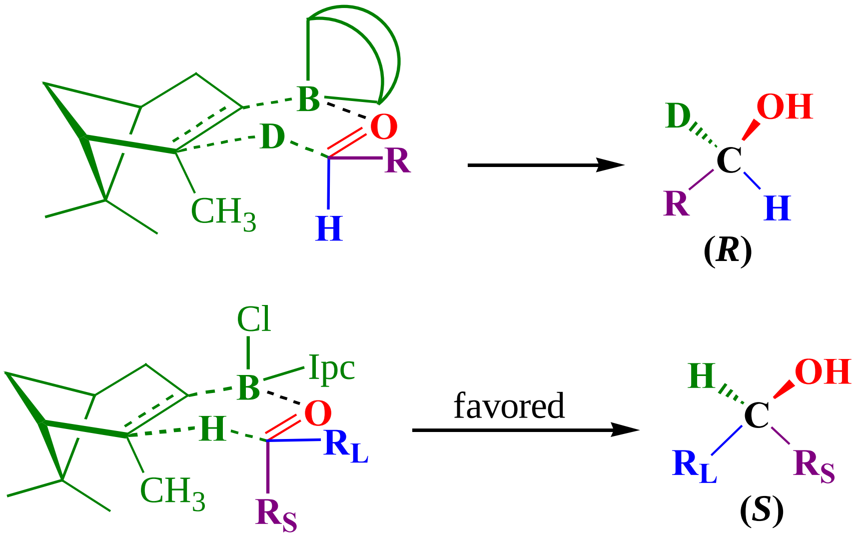
5. Chiral reducing agents:

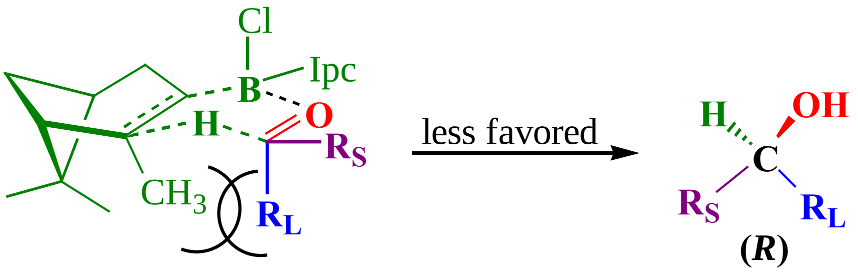
1) Chiral reducing agents derived from aluminum or boron reducing agents that involve one or more chiral organic ligands.

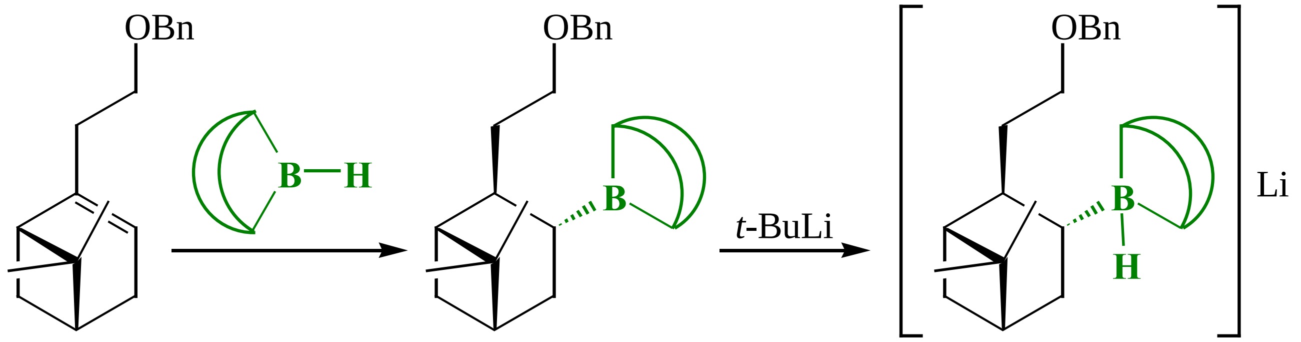
2) *S*-Alpine-borane and *R*-Alpine-borane are derived from either (–)-α-pinene or (+)-α-pinene and 9-borabicyclo[3.3.1]nonane (9-BBN).











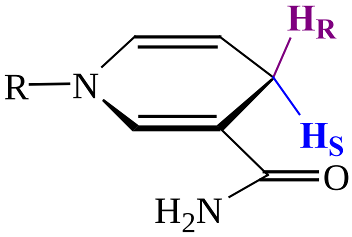
nopol benzyl ether **NB-Enantrane™** **NB-Enantride™**

3) Reagents derived from $LiAlH_4$ and chiral amines have also been developed.

4) Often it is necessary to test several reaction conditions in order to achieve optimal stereoselectivity.

5. **Prochirality**

1) For a given enzymatic reaction only one specific hydride from C4 in NADH is transferred.



Nicotinamide ring NADH, showing the pro-*R* and pro-*S* hydrogens

2) The hydrogens at C4 of NADH are **prochiral**.

3) **Pro-*R* and pro-*S* hydrogens:**

i) If the configuration is *R* when the hydrogen is "replaced" by a group of higher priority than hydrogen it is a **pro-*R* hydrogen**.

ii) If the configuration is *S* when the hydrogen is "replaced" by a group of higher priority than hydrogen it is a **pro-*S* hydrogen**.

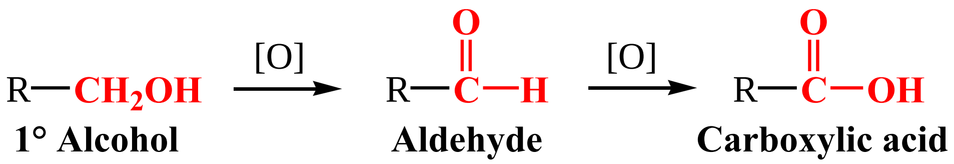
3) **Pro-chiral center:**

i) Addition of a group to a trigonal planar atom or replacement of one of two identical groups at a tetrahedral atom leads to a new stereocenter ⇒ a **prochiral center**.

12.4 OXIDATION OF ALCOHOLS

12.4A OXIDATION OF PRIMARY ALCOHOLS TO ALDEHYDES: $RCH_2OH \rightarrow RCHO$

1. 1° alcohols can be oxidized to aldehydes and carboxylic acids.

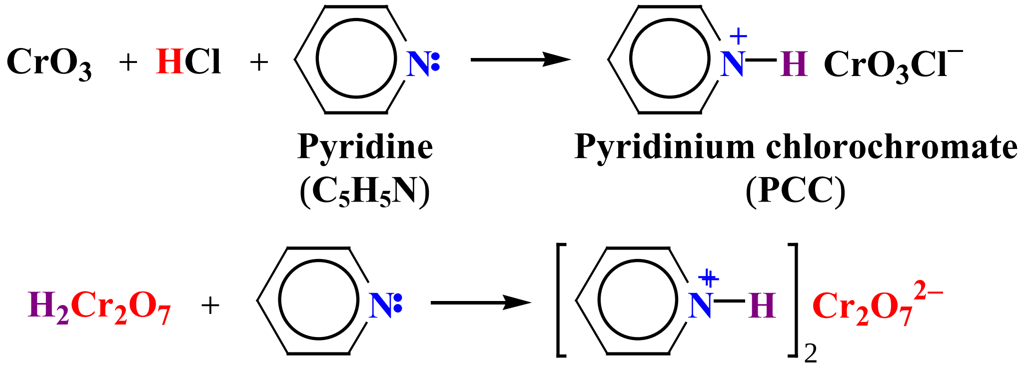


2. The oxidation of aldehydes to carboxylic acids in aqueous solutions usually takes place with less powerful agents than those required to oxidize 1° alcohols to aldehydes ⇒ it is difficult to stop the oxidation at the aldehyde stage.

1) Dehydrogenation of an organic compound corresponds to oxidation, whereas hydrogenation corresponds to reduction.

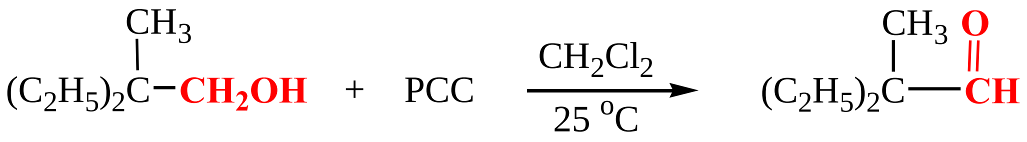
3. A variety of oxidizing agents are available to prepare aldehydes from 1° alcohols such as **pyridinium chlorochromate** (**PCC**) and **pyridinium dichromate** (**PDC**).

1) PCC is prepared by dissolving CrO_3 in hydrochloric acid and then treated with pyridine.



Pyridine **Pyridinium dichromate (PDC)**

2) PCC does not attack double bonds.



2-Ethyl-2-methyl-1-butanol **2-Ethyl-2-methylbutanal**

3) PCC and PDC are ***cancer suspect agents*** and must be dealt with care.

4. One reason for the success of oxidation with PCC is that the oxidation can be carried out in a solvent such as CH_2Cl_2, in which PCC is soluble.

1) Aldehydes themselves are not nearly so easily oxidized as are the ***aldehyde hydrates***, $RCH(OH)_2$, that form when aldehydes are dissolved in water, the usual medium for oxidation by PCC.

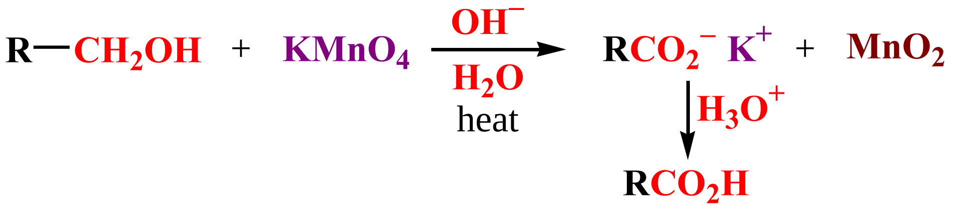
$$RCHO + H_2O \rightleftharpoons RCH(OH)_2$$

12.4B Oxidation of Primary Alcohols to Carboxylic Acids: $RCH_2OH \rightarrow RCO_2H$

1. 1° alcohols can be oxidized to carboxylic acids by potassium permanganate.

1) The reaction is usually carried out in basic aqueous solution from which MnO_2 precipitates as the oxidation takes place.

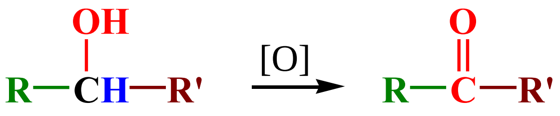
2) After the oxidation is complete, filtration allows removal of the MnO_2 and acidification of the filtrate gives the carboxylic acid.



12.4C Oxidation of Secondary Alcohols to Ketones

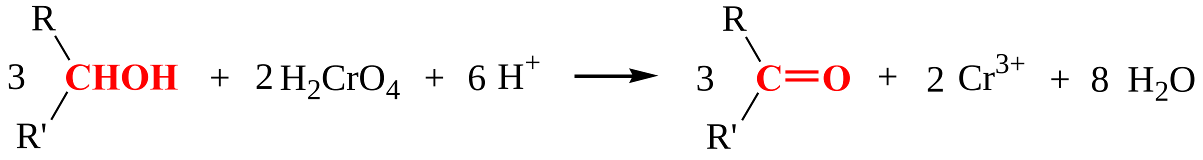
1. 2° alcohols can be oxidized to ketones.

1) The reaction usually stop at the ketone stage because further oxidation requires the breaking of a C–C bond.



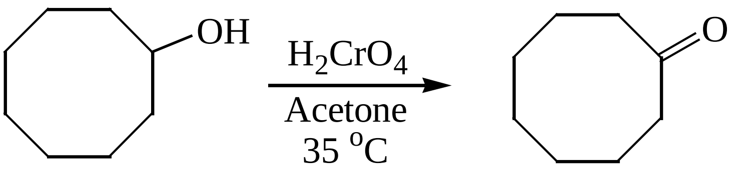
2° Alcohol **Ketone**

2. Various oxidizing agents based on chromium(VI) have been used to oxidize 2° alcohols to ketones.
   1) The most commonly used reagent is chromic acid (H_2CrO_4).
   2) Chromic acid is usually prepared by adding chromium(VI) oxide (CrO_3) or sodium dichromate ($Na_2Cr_2O_7$) to aqueous sulfuric acid.
   3) Oxidation of 2° alcohols are generally carried out in acetone or acetic acid solutions.



   4) As chromic acid oxidizes the alcohol to ketone, chromium is reduced from the +6 oxidation state (H_2CrO_4) to the +3 oxidation state (Cr^{3+}).

3. Chromic acid oxidations of 2° alcohols generally give ketones in excellent yields if the temperature is controlled.



Cyclooctanol **Cyclooctanone**

4. The use of CrO_3 in aqueous acetone is usually called the **Jones oxidation**.
   1) Jones oxidation rarely affects double bonds present in the molecule.

12.4D MECHANISM OF CHROMATE OXIDATION

1. The mechanism of chromic acid oxidations of alcohols:

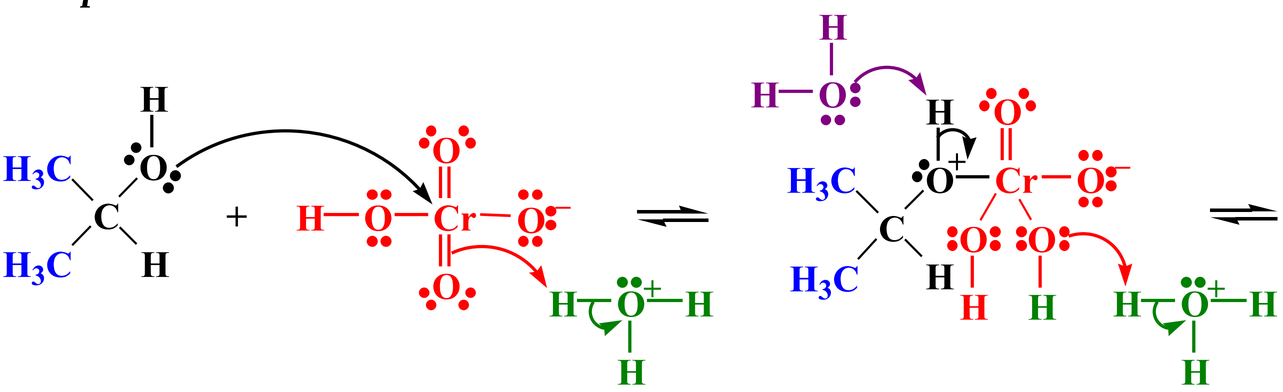
1) The first step is the formation of a chromate ester of the alcohol.

2) The chromate ester is unstable and is not isolated. It transfers a proton to a base (usually water) and simultaneously eliminates an $HCrO_3^-$ ion.

A Mechanism for the Reaction

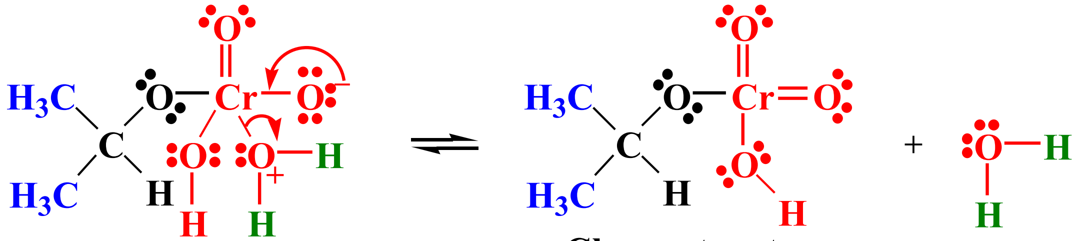
Chromate Oxidations: Formation of the Chromate Ester

Step 1



The alcohol donates an electron pair to the chromium atom, as an oxygen accepts a proton.

One oxygen loses a proton; another oxygen accepts a proton.



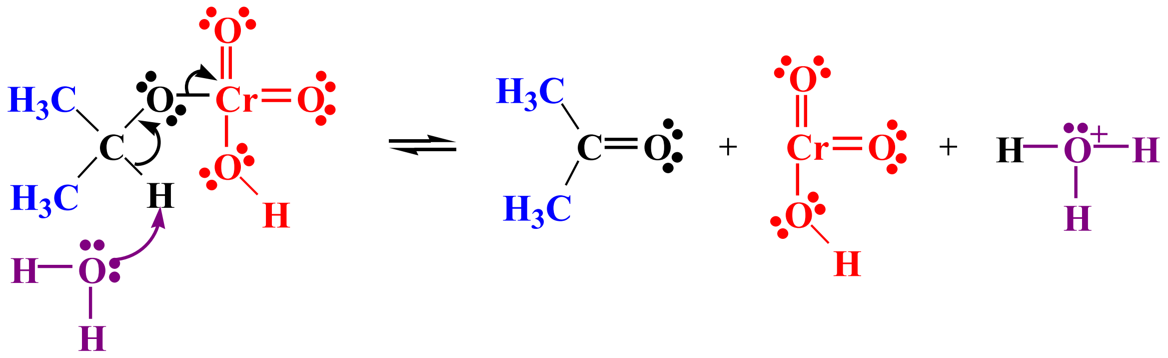
Chromate ester

A molecule of water departs as a leaving group as a chromium-oxygen double bond forms.

A Mechanism for the Reaction

Chromate Oxidations: The Oxidation Step

Step 2

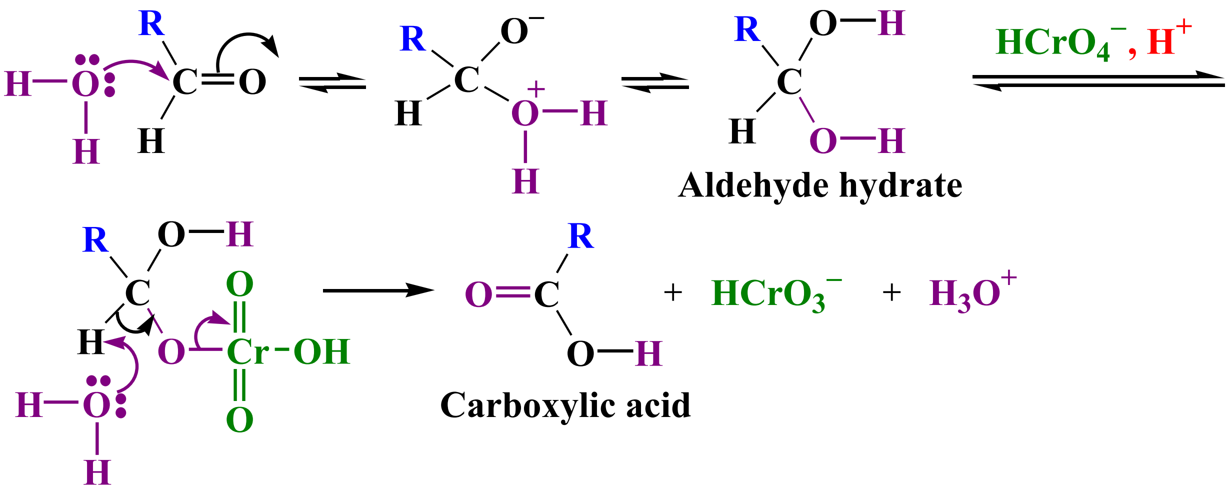


The chromium atom departs with a pair of electrons that formerly belonged to the alcohol; the alcohol is thereby oxidized and the chromium reduced.

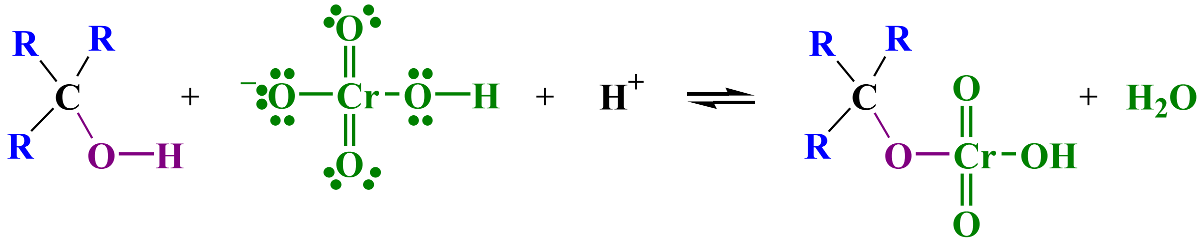
3) The overall result of second step is the reduction of $HCrO_4^-$ to $HCrO_3^-$, a two electron (2 e^-) change in the oxidation state of chromium, from Cr(VI) to Cr(IV).
4) At the same time the alcohol undergoes a 2 e^- oxidation to the ketone.
5) The remaining steps of the mechanism are complicated which involve further oxidations (and disproportionations), ultimately, converting Cr(IV) compounds to Cr^{3+} ions.

2. The aldehydes initially formed are easily oxidized to carboxylic acids in aqueous solutions.

1) The aldehyde initially formed from a 1° alcohol reacts with water to form an aldehyde hydrate.
2) The aldehyde hydrate can then react with $HCrO_4^-$ (and H^+) to form a chromate ester, and this can then be oxidized to the carboxylic acid.
3) In the absence of water (i.e., using PCC in CH_2Cl_2), the aldehyde hydrate does not form ⇒ further oxidation does not happen.



3. The chromate ester from 3° alcohols does not bear a hydrogen that can be eliminated, and therefore no oxidation takes place.

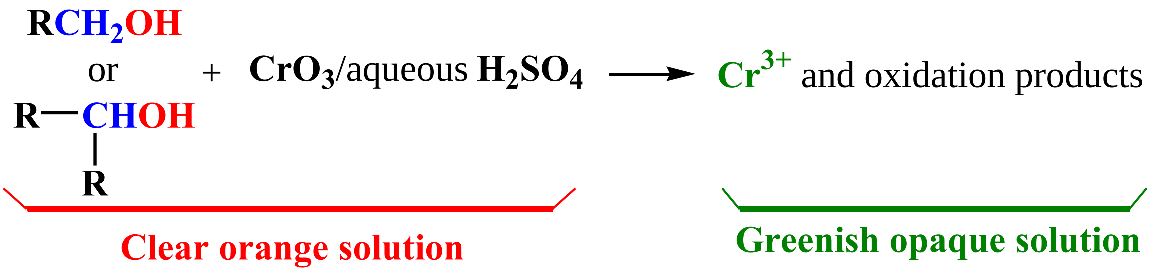


3°Alcohol

This chromate ester cannot undergo elimination of H_2CrO_3

12.4E A CHEMICAL TEST FOR PRIMARY AND SECONDARY ALCOHOLS

1. The relative ease of oxidation of 1° and 2° alcohols compared with the difficulty of oxidizing 3° alcohols forms the basis for a convenient chemical test.
   1) 1° and 2° alcohols are rapidly oxidized by a solution of CrO_3 in aqueous sulfuric acid.
   2) Chromic oxide (CrO_3) dissolves in aqueous sulfuric acid to give a clear orange solution containing $Cr_2O_7^{2-}$ ions.
   3) A positive test is indicated when this clear orange solution becomes opaque and takes on a greenish cast within 2 s.



i) **This color change, associated with the reduction of $Cr_2O_7^{2-}$ to Cr^{3+}, forms the basis for "Breathalyzer tubes" used to detect intoxicated motorists. In the Breathalyzer the dichromate salt is coated on granules of silica gel.**

ii) This test not only can distinguish 1° and 2° alcohols from 3° alcohols it also can distinguish them from other compounds except aldehydes..

12.4F Spectroscopic Evidence for Alcohols

1. Alcohols give rise to O–H stretching absorptions from 3200 to 3600 cm^{-1} in infrared spectra.
2. The alcohol hydroxyl hydrogen typically produced a broad ^1H NMR signal of variable chemical shift which can be eliminated by exchange with deuterium from D_2O.

3) The ^{13}C NMR spectrum of an alcohol sows a signal between δ 50 and δ 90 for the alcohol carbon.

4) Hydrogen atoms on the carbon of a 1° or 2° alcohol produce a signal in the ^1H NMR spectrum between δ 3.3 and δ 4.0 that integrates for 2 or 1 hydrogens, respectively

12.5 Organometallic Compounds

1. Compounds that contain carbon-metal bonds are called **organometallic compounds**.

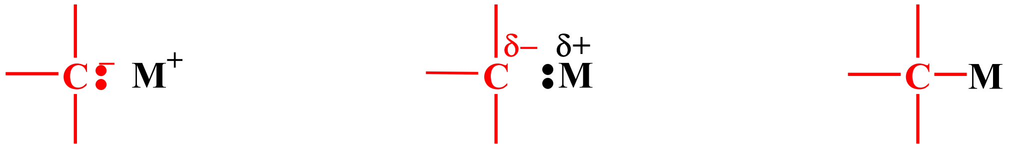
   1) The nature of the C–M bond varies widely, ranging from bonds that are essentially ionic to those that are primarily covalent.

2) The structure of the organic portion of the organometallic compound has some effects on the nature of the C–M bond, the identity of the metal itself is of far greater importance.

i) C–Na and C–K bonds are largely ionic in character.

ii) C–Pb, C–Sn, C–Tl, and C–Hg bonds are essentially covalent.

iii) C–Li and C–Mg bonds lie in between these two extremes.



Primarily ionic
(M = Na^+ or K^+)

(M = Mg or Li)

Primarily covalent
(M = Pb, Sn, Hg, or Tl)

2. The reactivity of organometallic compounds increases with the percent ionic character of the C–M bond.

1) Alkylsodium and alkylpotassium compounds are highly reactive and are among the most powerful of bases ⇒ they react explosively with water and burst into flame when exposed to air.

2) Organomercury and organolead compounds are much less reactive ⇒ they are often volatile and are stable in air.

i) They are all poisonous and are generally soluble in nonpolar solvents.

ii) Tetraethyllead has been replaced by other antiknock agent such as *tert*-butyl methyl ether (TBME).

3. Organolithium and organomagnesium compounds are of great importance in organic synthesis.

i) They are relatively stable in ether solutions.

iii) Their C–M bonds have considerable ionic character ⇒ the carbon atom that is bonded to the metal atom of an organolithium or organomagnesium compound is a strong base and powerful nucleophile.

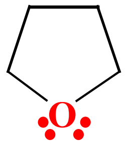
12.6 Preparation of Organolithium and Organomagnesium Compounds

12.6A Organolithium Compounds

1. Organolithium compounds are often prepared by the reduction of organic halide with lithium metal.
   1) These reductions are usually carried out in ether solvents and care must be taken to exclude moisture since organolithium compounds are strong bases.
      i) Most commonly used solvents are diethyl ether and tetrahydrofuran.

$CH_3CH_2\ddot{\underset{\cdot\cdot}{O}}CH_2CH_3$

Diethyl ether
(Et_2O)



Tetrahydrofuran
(THF)

      ii) Most organolithium compounds slowly attack ethers by bringing about an elimination reaction.

$$\overset{\delta-}{R}:\overset{\delta+}{Li} + H{-}CH_2{-}CH_2{-}OCH_2CH_3 \longrightarrow RH + H_2C{=}CH_2 + Li^{+}\,{}^{-}OCH_2CH_3$$

      iii) Ether solutions of organolithium reagents are not usually stored but are used immediately after preparation.
      iv) Organolithium compounds are much more stable in hydrocarbon solvents.

   2) Examples of organolithium compounds prepared in ether

$$CH_3CH_2CH_2CH_2Br + 2\ \mathbf{Li} \xrightarrow[Et_2O,\ 80\text{-}90\%]{-10\ ^{o}C} CH_3CH_2CH_2CH_2\mathbf{Li} + LiBr$$

Butyl bromide → **Butyllithium**

$$R{-}X + 2\ \mathbf{Li} \xrightarrow{Et_2O} R{-}\mathbf{Li} + LiX$$

(or **Ar–X**) → (or **ArLi**)

   3) The order of reactivity of halides is RI > RBr > RCl (Alkyl and aryl fluorides are seldom used in the preparation of organolithium compounds).

12.6B GRIGNARD REAGENTS

1. Organomagnesium halides were discovered by the French chemist Victor Grignard in 1900.
   1) Grignard received the Nobel Prize in 1912 and organomagnesium halides are now called **Grignard reagents**.
   2) Grignard reagents have great use in organic synthesis.

2. Grignard reagents are usually prepared by the reaction of an organohalide and magnesium metal (turnings) in an ether solvent.

$$\left.\begin{array}{l} \mathbf{R}X + Mg \xrightarrow{Et_2O} \mathbf{R}MgX \\ \mathbf{Ar}X + Mg \xrightarrow{Et_2O} \mathbf{Ar}MgX \end{array}\right\} \textbf{Grignard reagents}$$

   1) The order of reactivity of halides with magnesium is RI > RBr > RCl (very few organomagnesium fluorides have been prepared).
      i) Aryl Grignard reagents are more easily prepared from aryl bromides and aryl iodides than from aryl chlorides, which react very sluggishly.

3. Grignard reagents are seldom isolated but are used for further reactions in ether solution.

$$\mathbf{CH_3}X + Mg \xrightarrow[35\ ^{o}C]{Et_2O} \mathbf{CH_3}MgX$$

Methylmagnesium iodide (95%)

$$\mathbf{C_6H_5}X + Mg \xrightarrow[35\ ^{o}C]{Et_2O} \mathbf{C_6H_5}MgX$$

Phenylmagnesium bromide (95%)

4. The actual structures of Grignard reagents are more complex than the general formula RMgX indicates.
   1) Experiments done with radioactive magnesium have established that, for most

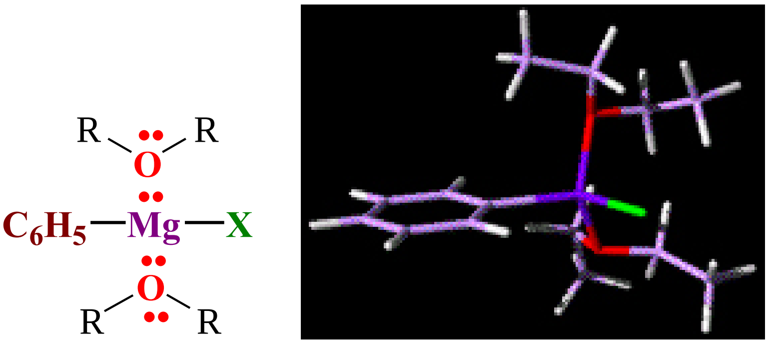
Grignard reagents, there is an equilibrium between an alkylmagnesium halide and a dialkylmagnesium.

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2$$

Alkylmagnesium halide → **Dialkylmagnesium**

2) For convenience, RMgX is used for the Grignard reagent.

5. A Grignard reagent forms a complex with its ether solvent:



1) Complex formation with molecules of ether is an important factor in the formation and stability of Grignard reagents.

2) Organomagnesium compounds can be prepared in nonethereal solvents, but the preparations are more difficult.

6. The mechanism for the formation of Grignard reagents might involve radicals:

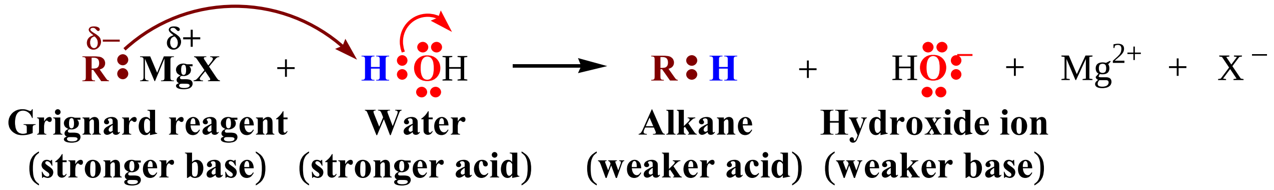
$$R{-}X + :Mg \longrightarrow R\bullet + \bullet MgX$$
$$R\bullet + \bullet MgX \longrightarrow RMgX$$

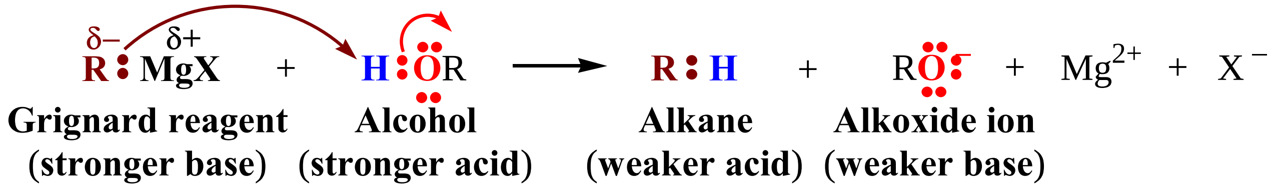
12.7 Reactions of Organolithium and Organomagnesium Compounds

12.7A Reactions with Compounds Containing Acidic Hydrogen Atoms

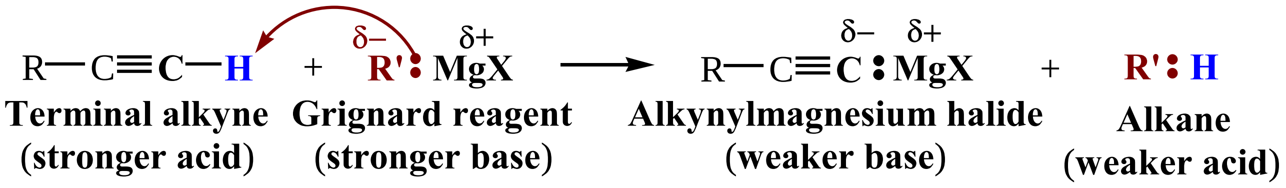
1. Grignard reagents and organolithium compounds are very strong bases ⇒ they react with any compound that has a hydrogen attached to an electronegative atom such as oxygen, nitrogen, or sulfur.

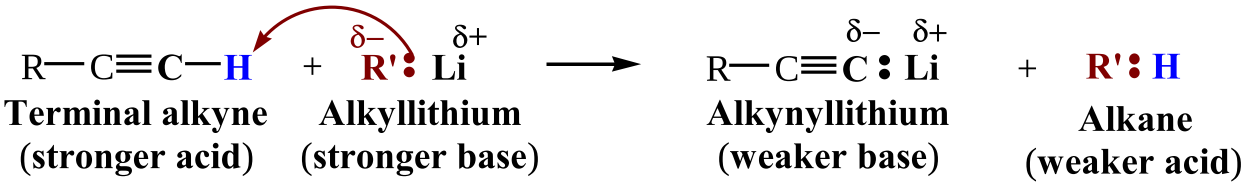
1) The reactions of Grignard reagents with water and alcohols are simply acid-base reactions ⇒ the Grignard reagent behaves as if it contained an **carbanion**.





2) Grignard reagents and organolithium compounds abstract protons that are much less acidic than those of water and alcohols ⇒ a useful way to prepare **alkynylmagnesium halides** and **alkynyllithium**.

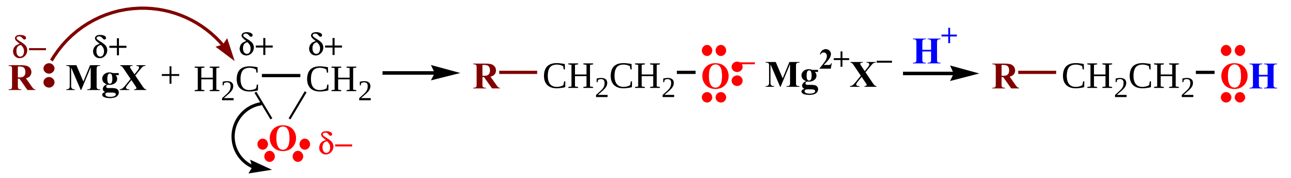




2. Grignard reagents and organolithium compounds are powerful nucleophiles.

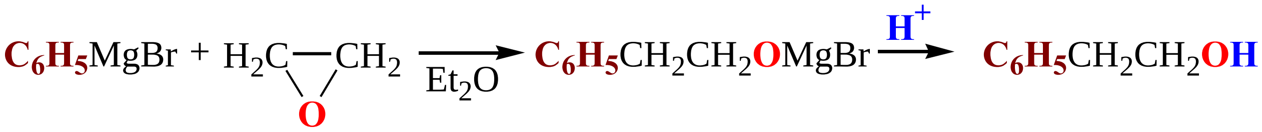
12.7B Reactions of Grignard Reagents with Oxiranes (Epoxides)

1. Grignard reagents carry out nucleophilic attack at a saturated carbon when they react with oxiranes ⇒ a convenient way to synthesize 1° alcohols.



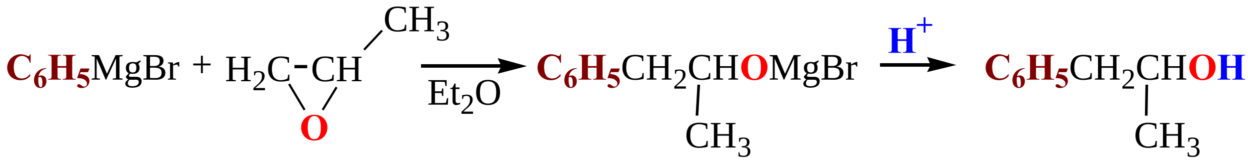
Oxirane A primary alcohol

Specific Examples



1) Grignard reagents react primarily at the less-substituted ring carbon of substituted oxirane.

Specific Examples



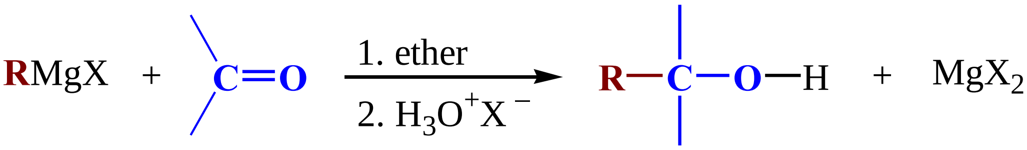
12.7C Reactions of Grignard Reagents with Carbonyl Compounds

1. The most important reactions of Grignard reagents and organolithium compounds are the nucleophilic attack to the carbonyl group.

A Mechanism for the Reaction

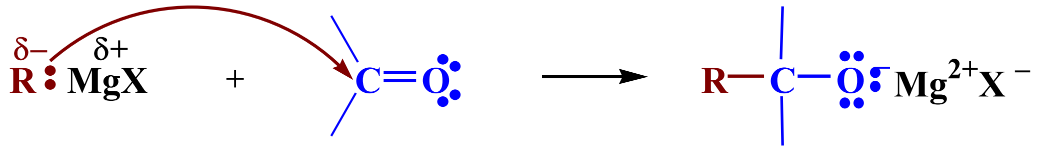
The Grignard Reaction

Reaction:



Mechanism:

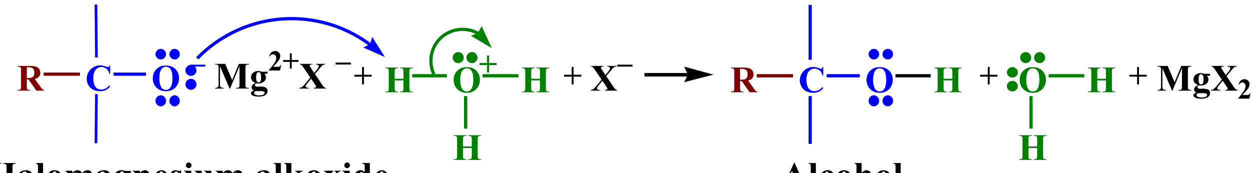
Step 1



Grignard reagent Carbonyl compound Halomagnesium alkoxide

The strongly nucleophilic Grignard reagent uses its electron pair to form a bond to the carbon atom. One electron pair of the carbonyl group shifts out to the oxygen. This reaction is a nucleophilic addition to the carbonyl group, and it results in the formation of an alkoxide ion associated with Mg^{2+} and X^{-}.

Step 2

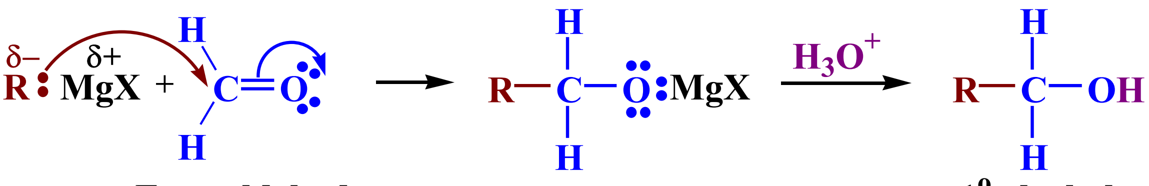


Halomagnesium alkoxide Alcohol

In the second step, the addition of aqueous HX causes protonation of the alkoxide ion; this leads to the formation of the alcohol and MgX_2.

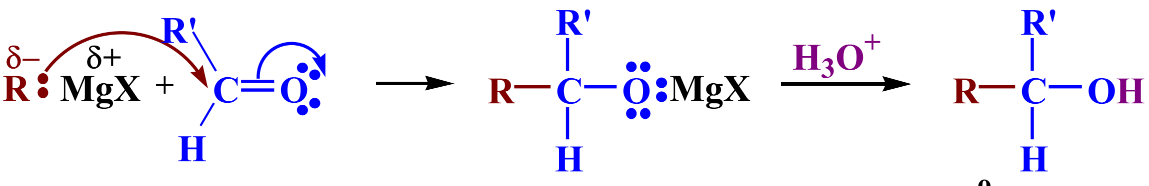
12.8 ALCOHOLS FROM GRIGNARD REAGENTS

1. Grignard Reagents React with Formaldehyde to Give a 1° Alcohol.



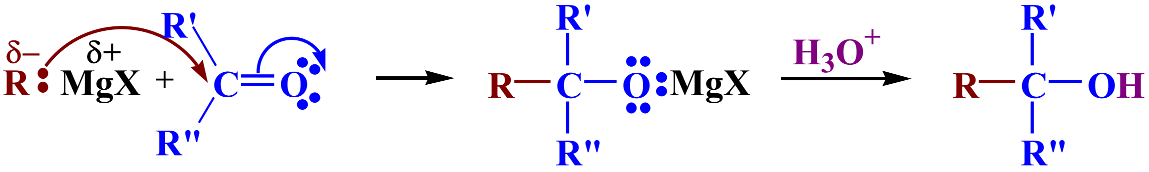
Fromaldehyde 1^{o} alcohol

2. Grignard Reagents React with All Other Aldehydes to Give 2° Alcohols.



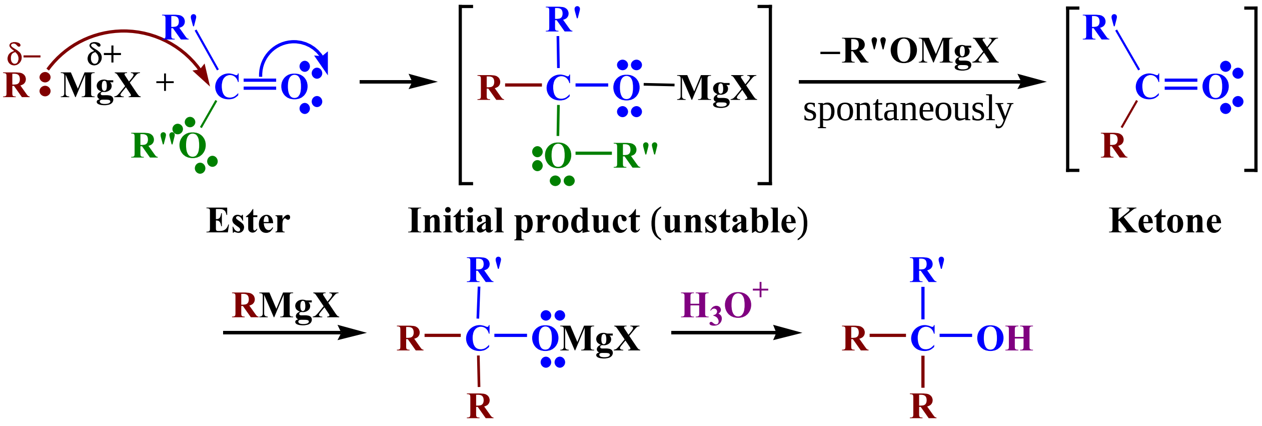
Higher aldehyde 2^{o} alcohol

3. Grignard Reagents React with Ketones to Give 3° Alcohols.



Ketone — 3° alcohol

4. Esters React with Two Molar Equivalents of a Grignard Reagent to Form 3° Alcohols.



Ester — Initial product (unstable) — Ketone

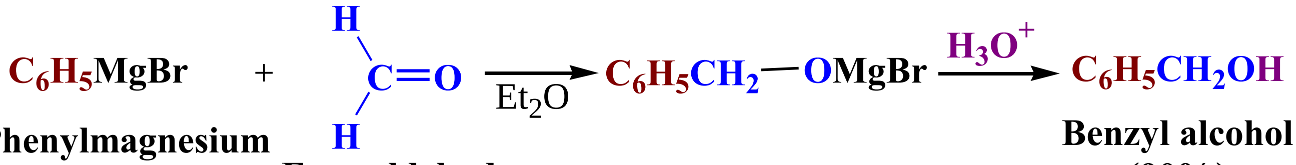
Salt of an alcohol (not isolated) — 3° alcohol

1) The initial addition product is unstable and loses a magnesium alkoxide to form a ketone which is more reactive toward Grignard reagents than esters.
2) A second molecule of the Grignard reagentadds to the carbonyl group as soon as the ketone is formed in the mixture.
3) After hydrolysis, **the product is a 3° alcohol with two identical alkyl groups**.

SPECIFIC EXAMPLES

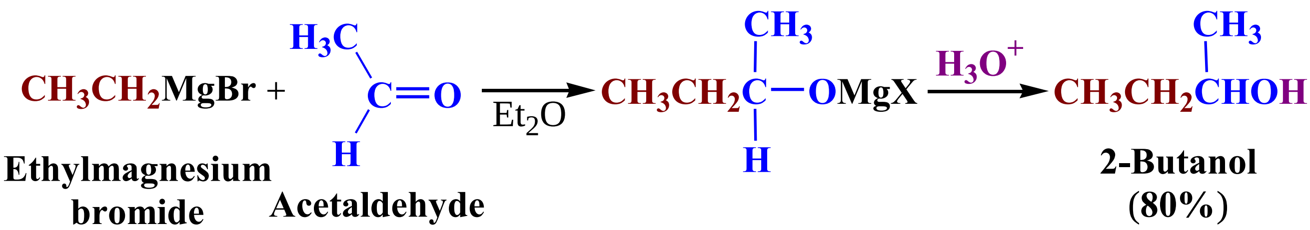
GRIGNARD REAGENT	CARBONYL REACTANT	FINAL PRODUCT

Reaction with formaldehyde

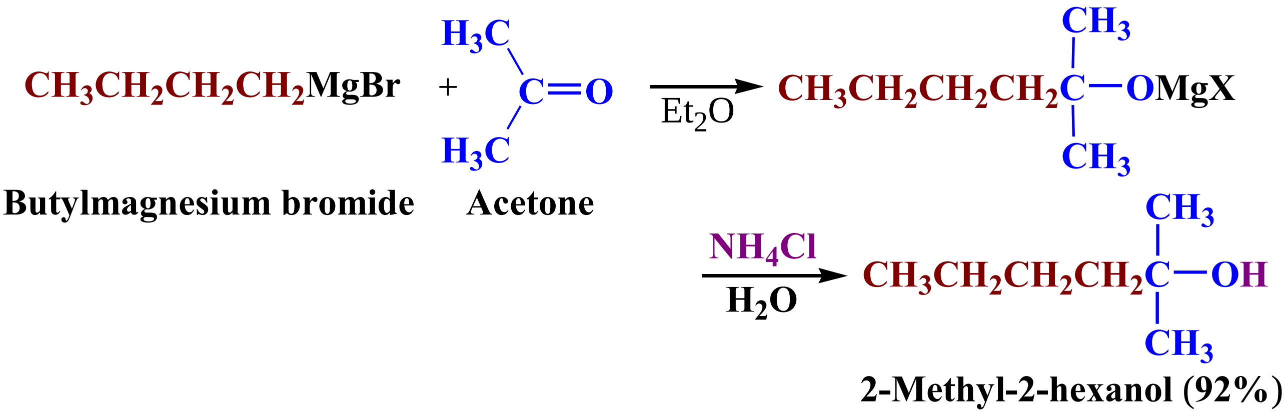


Phenylmagnesium bromide — Fromaldehyde — Benzyl alcohol (90%)

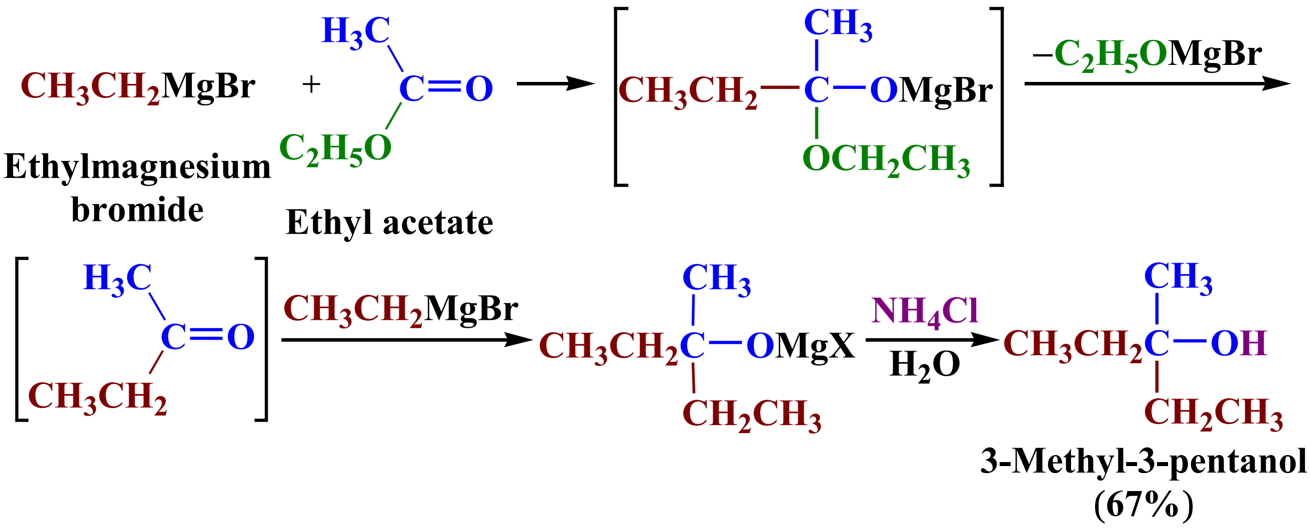
Reaction with a higher aldehyde



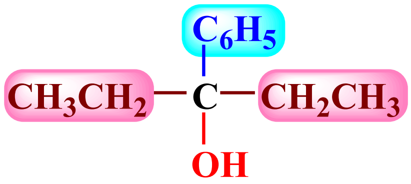
Reaction with a ketone



Reaction with an ester



12.8A PLANNING A GRIGNARD SYNTHESIS

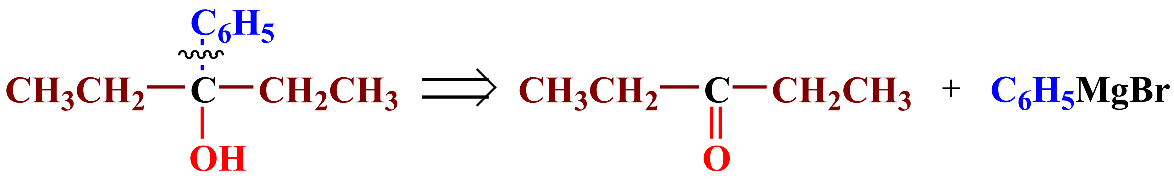


3-Phenyl-3-pentanol

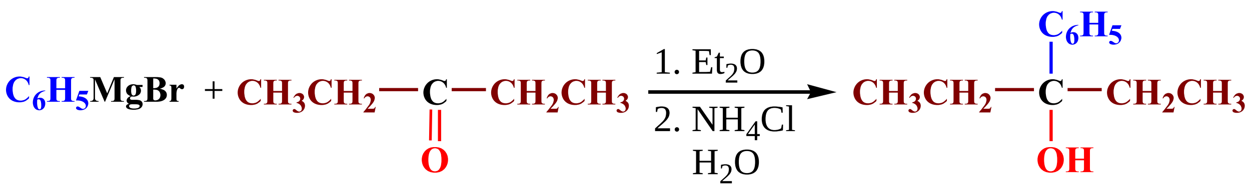
1. We can use a ketone with two ethyl groups (3-pentanone) and allow it to react

with phenylmagnesium bromide:

Analysis



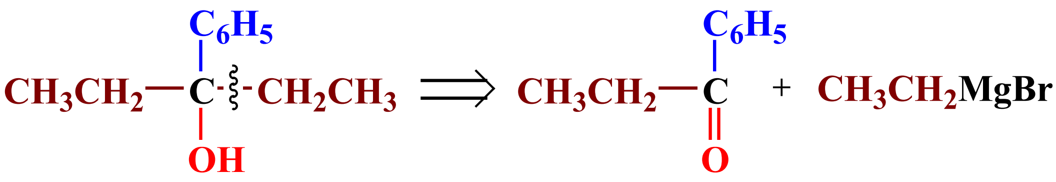
Synthesis



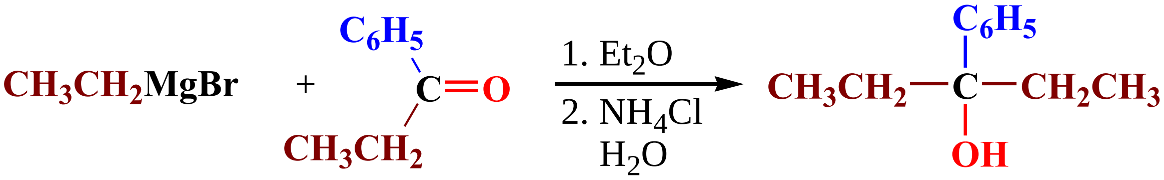
Phenylmagnesium bromide **3-Pentanone** **3-Phenyl-3-pentanol**

2. We can use a ketone containing an ethyl groups and a phenyl group (ethyl phenyl ketone) and allow it to react with ethylmagnesium bromide:

Analysis



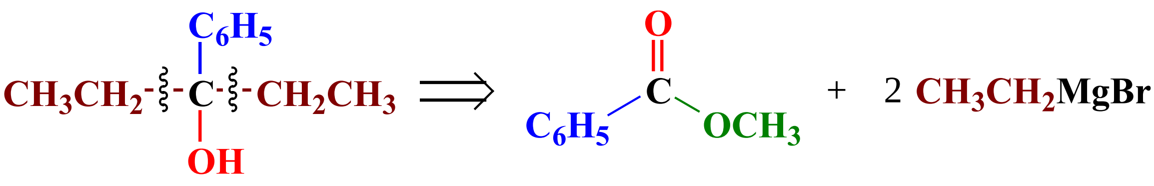
Synthesis



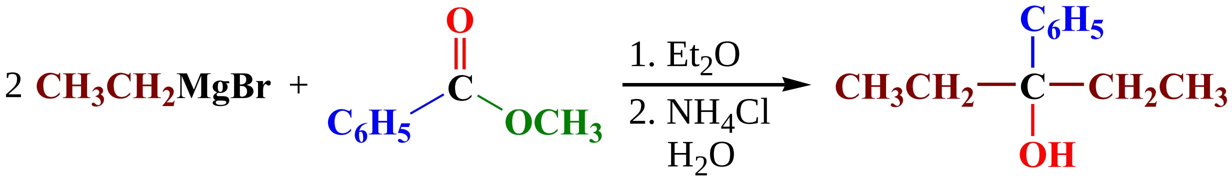
Ethylmagnesium bromide **Ethyl phenyl ketone** **3-Phenyl-3-pentanol**

3. We can use an ester of benzoic acid and allow it to react with two molar equivalents of ethylmagnesium bromide:

Analysis



Synthesis

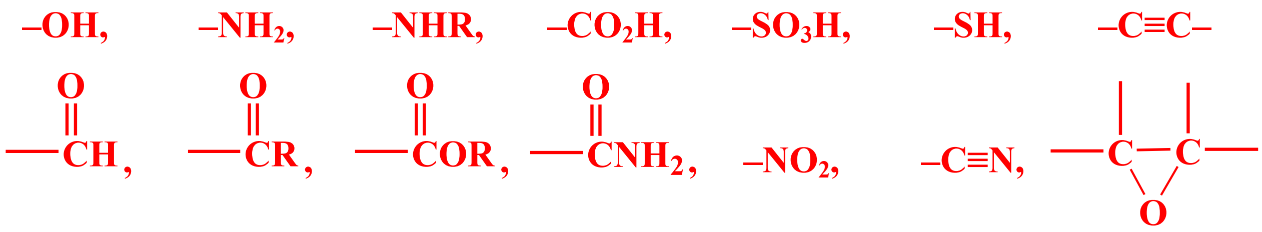


Ethylmagnesium bromide **Methyl benzoate** **3-Phenyl-3-pentanol**

4. All these methods will be likely to give the desired compound in greater than 80% yields.

12.8B Restrictions on the Use of Grignard Reagents

1. ***The Grignard reagent is a very powerful base*** ⇒ it is not possible to prepare a Grignard reagent from an organic group that contains an ***acidic hydrogen***.
2. ***Grignard reagents are powerful nucleophiles*** ⇒ it is not possible to prepare a Grignard reagent from any organic halide that contains a carbonyl, epoxy, nitro, or cyano group.



Grignard reagents containing these groups cannot be prepared.

This means that when we prepare Grignard reagents, we are effectively limited to alkyl halides or tro analogous organic halides containing C=C bonds, internal triple bonds, ether linkages, and –NR$_2$ groups.

3. Grignard reactions are so sensitive to acidic compounds that special care must be taken to exclude moisture from the apparatus and anhydrous ether must be used as the solvent.

4. Acetylenic Grignard reagents:

$$C_6H_5C{\equiv}CH + C_2H_5MgBr \longrightarrow C_6H_5C{\equiv}CMgBr + C_2H_6\text{¡ô}$$

$$C_6H_5C{\equiv}CMgBr + C_2H_5\overset{\overset{\displaystyle O}{\|}}{C}H \xrightarrow[\substack{2.\ H_3O^+ \\ (\mathbf{52}\ \%)}]{} C_6H_5C{\equiv}C-\underset{\underset{\displaystyle OH}{|}}{C}HC_2H_5$$

5. Care must be taken in designing syntheses involving Grignard reagents ⇒ the reacting electrophile can not contain an acidic group.

   1) The following reaction would take place when 4-hydroxy-2-butanone is treated with methylmagnesium bromide:

$$CH_3MgBr + \underset{\textbf{4-Hydroxy-2-butanone}}{HOCH_2CH_2\underset{\underset{\displaystyle O}{\|}}{C}CH_3} \longrightarrow CH_4\text{¡ô} + BrMgOCH_2CH_2\underset{\underset{\displaystyle O}{\|}}{C}CH_3$$

   rather than:

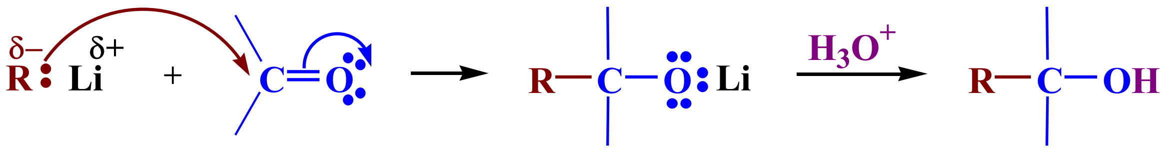
$$CH_3MgBr + HOCH_2CH_2\underset{\underset{\displaystyle O}{\|}}{C}CH_3 \;\not\longrightarrow\; HOCH_2CH_2\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OMgBr}{|}}{C}}CH_3$$

   2) Two equivalents of methylmagnesium bromide can be utilized to effect the following reaction:

$$HOCH_2CH_2\underset{\underset{\displaystyle O}{\|}}{C}CH_3 \xrightarrow[-\ CH_4]{2\ CH_3MgBr} BrMgOCH_2CH_2\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OMgBr}{|}}{C}}CH_3 \xrightarrow[H_2O]{2\ NH_4Cl} HOCH_2CH_2\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}CH_3$$

12.8C The Use of Lithium Reagents

1. Organolithium reagents (Rli) react with carbonyl compounds in the same way as Grignard reagents.



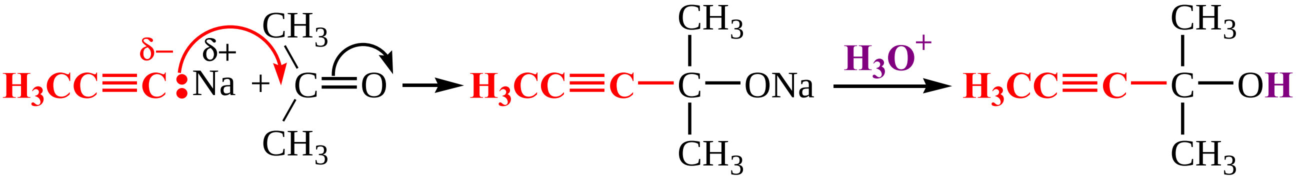
Organolithium reagent   Aldehyde or ketone   Lithium alkoxide   Alcohol

1) Organolithium reagents are somewhat **more reactive** than Grignard reagents.

12.8D THE USE OF SODIUM ALKYNIDES

1. Sodium alkynides react with aldehydes and ketones to yield alcohols.

$$H_3CC{\equiv}CH \xrightarrow[-NH_3]{NaNH_2} H_3CC{\equiv}CNa$$



12.9 LITHIUM DIALKYLCUPERATES: THE COREY-POSNER, WHITESIDES-HOUSE SYNTHESIS

1. A highly versatile method for the synthesis of alkanes and other hydrocarbons from organic halides has been developed by E. J. Corey (Harvard University, Nobel Prize for Chemistry in 1990), G. H. Posner (The Johns Hopkins University), and by G. M. Whitesides (Harvard University) and H. O. House (Georgia Institute of Technology).

$$\mathbf{R{-}X} + \mathbf{R'{-}X} \xrightarrow[(-\,2\ \mathbf{X})]{\text{several steps}} \mathbf{R{-}R'}$$

1) The transformation of an alkyl halide into a lithium dialkylcuprate (R_2CuLi) requires two steps:

i) The alkyl halide is treated with lithium metal in an ether solvent to give an alkyllithium, RLi.

$$\text{R—X} + 2\,\text{Li} \xrightarrow{\text{diethyl ether}} \underset{\textbf{Alkyllithium}}{\text{RLi}} + \text{LiX}$$

ii) Then the alkyllithium is treated with cuprous iodide (CuI) to furnish the lithium dialkylcuprate.

$$\underset{\textbf{Alkyllithium}}{2\,\text{RLi}} + \text{CuI} \longrightarrow \underset{\textbf{Lithium dialkylcuprate}}{\text{R}_2\text{CuLi}} + \text{LiI}$$

2) One alkyl group of the lithium dialkylcuprate undergoes a coupling reaction with the second alkyl halide (R’–X) to afford an alkane.

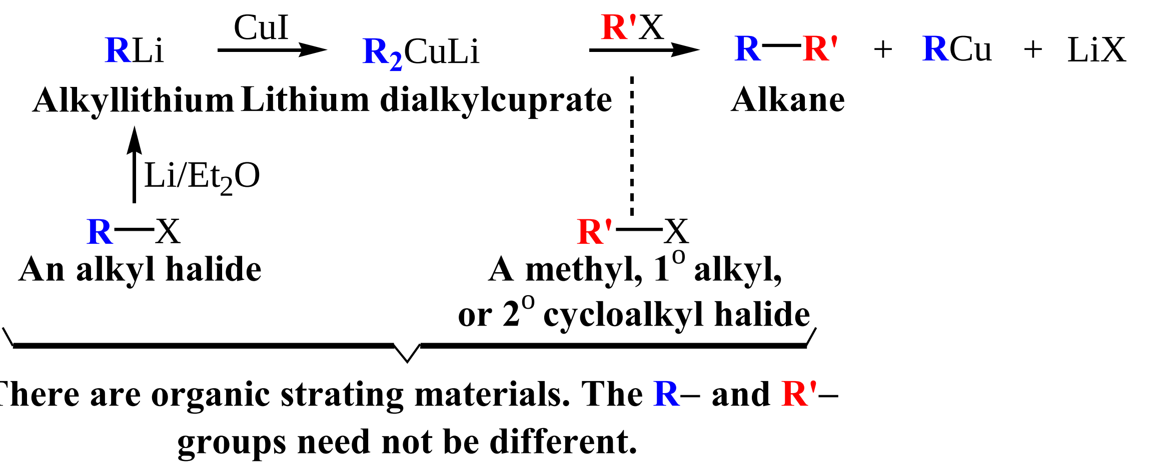
$$\underset{\textbf{Lithium dialkylcuprate}}{\text{R}_2\text{CuLi}} + \underset{\textbf{Alkyl halide}}{\text{R'—X}} \longrightarrow \underset{\textbf{Alkane}}{\text{R—R'}} + \text{RCu} + \text{LiX}$$

i) For the last step to give a good yield of the alkane, the alkyl halide R’–X must be either a methyl halide, a 1° alkyl halide, or a 2° cycloalkyl halide.

ii) The alkyl groups of the lithium dialkylcuprate may be methyl, 1°, 2°, or 3°.

iii) The two alkyl groups being coupled need not be different.

3) The overall scheme for this alkane synthesis:



4) Examples:

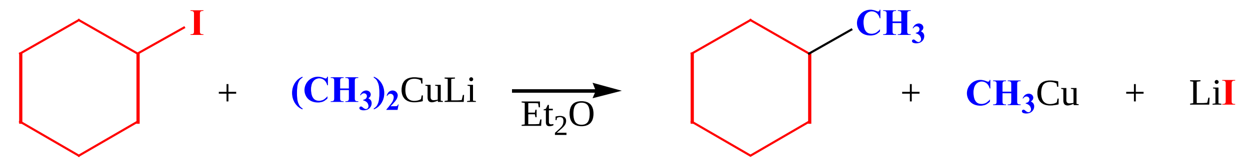
$$\text{H}_3\text{C—I} \xrightarrow[\text{Et}_2\text{O}]{\text{Li}} \text{CH}_3\text{Li} \xrightarrow{\text{CuI}} (\text{CH}_3)_2\text{CuLi} \xrightarrow{\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I}} \underset{\textbf{Hexane (98 \%)}}{\text{H}_3\text{C—CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3}$$

$$CH_3CH_2CH_2CH_2Br \xrightarrow[Et_2O]{Li} CH_3CH_2CH_2CH_2Li \xrightarrow{CuI} (CH_3CH_2CH_2CH_2)_2CuLi$$

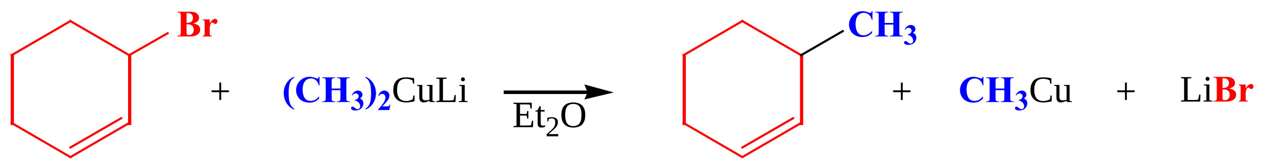
$$\xrightarrow{CH_3CH_2CH_2CH_2CH_2Br} H_3CH_2CH_2CH_2C{-}CH_2CH_2CH_2CH_2CH_3$$

Nonane
(98 %)

2. Lithium dialkylcuprates couple with other organic groups:

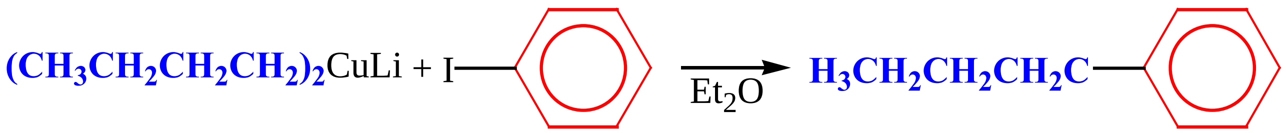


Methylcyclohexane
(75 %)



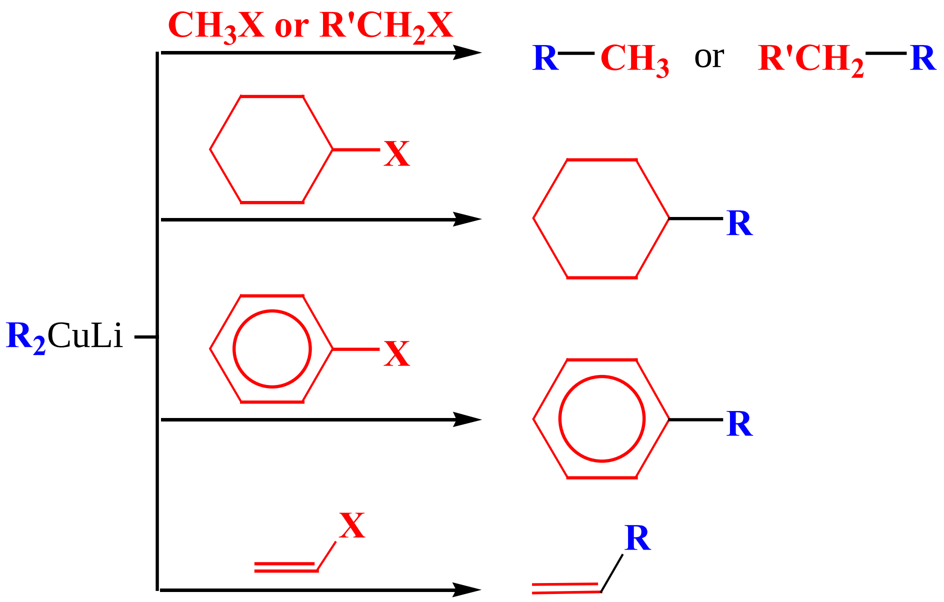
3-Methylcyclohexene
(75 %)

1) Lithium dialkylcuprates couple with phenyl and vinyl halides:



Butylbenzene
(75 %)

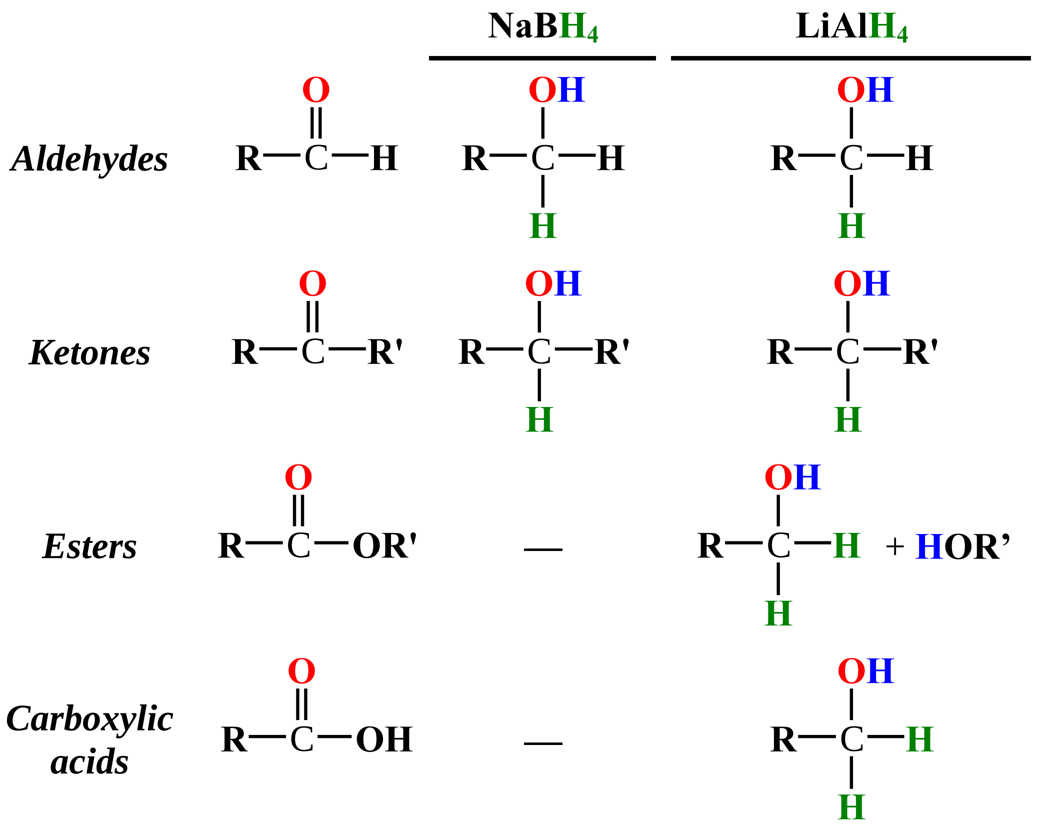
3. Summary of the coupling reactions of lithium dialkylcuprates:



12.10 Protecting Groups

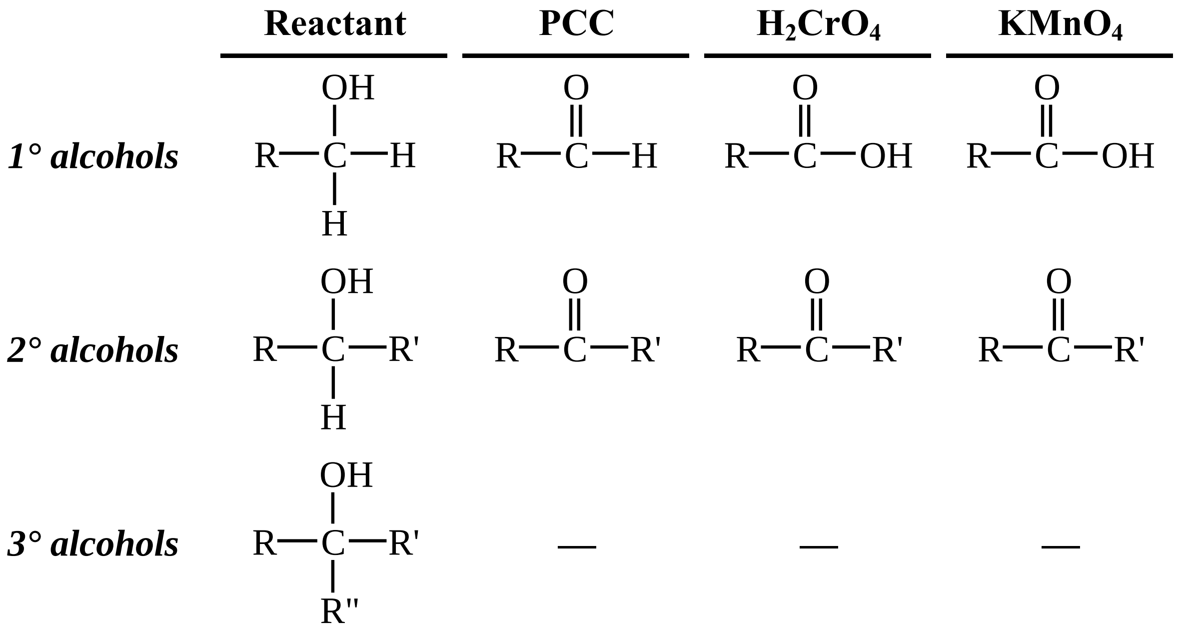
12.11 Summary of Reactions

12.11A Overall Summary of Reduction Reactions (Section 12.3)



Hydrogens in **blue** are added during the reaction workup by water or aqueous acid.

12.11B Overall Summary of Oxidation Reactions (Section 12.4)

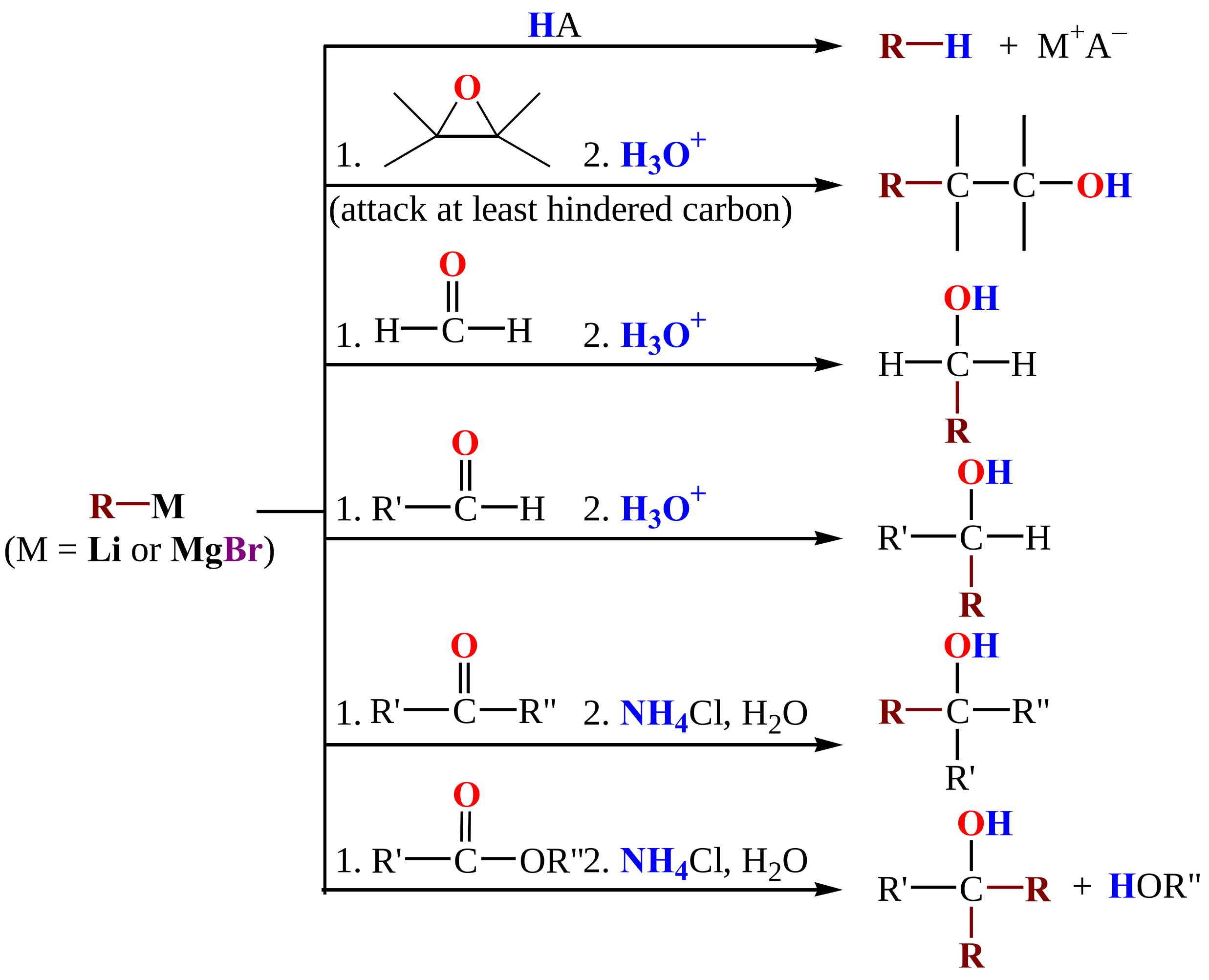


12.11C Formation of Organolithium and Grignard Reagents (Section 12.3)

$$R{-}X + 2\,Li \longrightarrow R{-}Li + LiX$$

$$R{-}X + Mg \longrightarrow R{-}MgX$$

12.11D Reactions of Grignard and Organolithium Reagents (Section 12.7 and 12.8)



12.11E Corey-Posner, Whiteside-House Synthesis (Section 12.9)

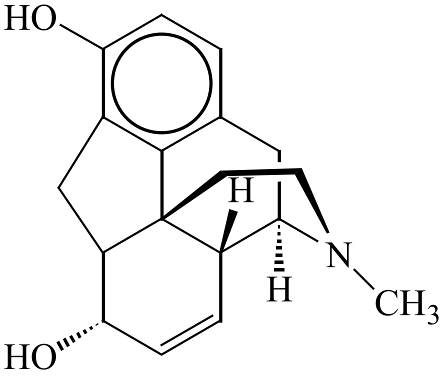
$$2\,RLi + CuI \longrightarrow R_2CuLi \xrightarrow[\text{(R' = 1}^{o}\text{ or 2}^{o}\text{, cyclic)}]{R'{-}X} R{-}R' + RCu + LiX$$

CONJUGATED UNSATURATED SYSTEMS

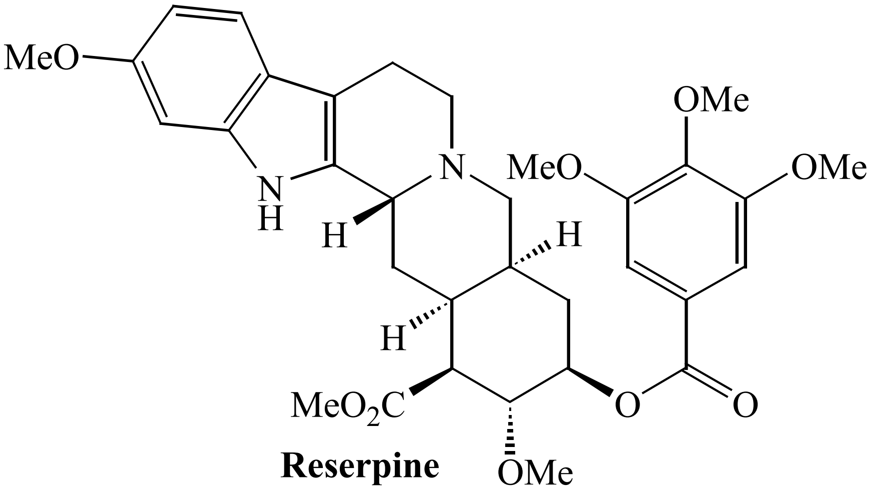
MOLECULES WITH THE NOBEL PRIZE IN THEIR SYNTHETIC LINEAGE (ANCESTRY)

1. The Diels-Alder reaction:
   1) Otto Diels and Kurt Alder won the Nobel Prize for Chemistry in 1950 for developing this reaction.
   2) It can form a six-membered ring with as many as four new stereocenters created in a single stereospecific step from acyclic precursors.
   3) It also produces a double bond that can be used to introduce other functionality.

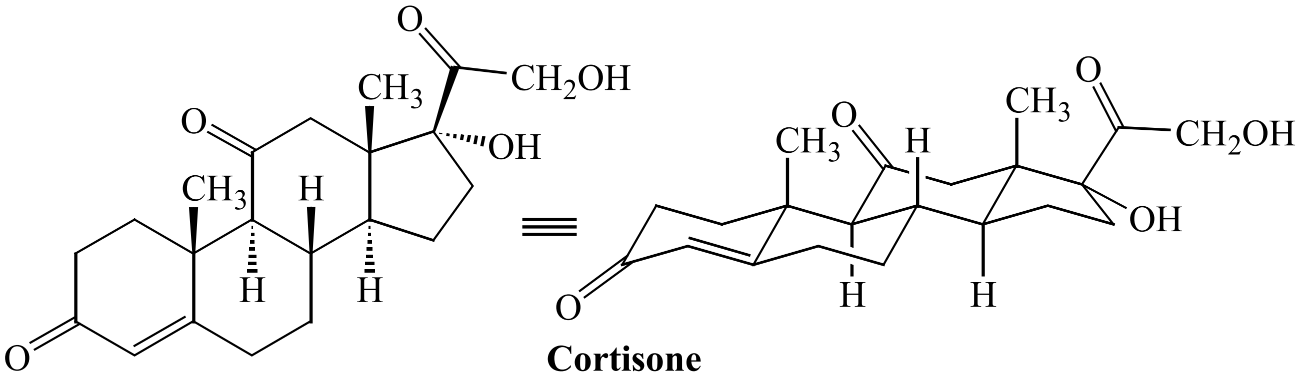
2. Molecules that have been synthesized using Diels-Alder reaction include:



Morphine



Reserpine



Cortisone

   1) Morphine (M. Gates): the hypnotic sedative used after many surgical procedures.
   2) Reserpine (R. B. Woodward): a clinically used antipypertensive agent.
   3) Chlesterol (R. B. Woodward): precursor of all steroids in the body.

Cortisone (R. B. Woodward): an antiinflammatory agent.

4) Prostaglandins $F_{2\alpha}$ and E_2 (E. J. Corey): members of a family of hormones that mediate blood pressure, smooth muscle contraction, and inflammation (Section 13.11D).

5) Vitamin B_{12} (A. Eschenmoser and R. B. Woodward): used in the production of blood and nerve cells (Section 4.20).

6) Taxol (K. C. Nicolaou): a potent cancer chemotherapy agent.

13.1 INTRODUCTION

1. ***Species that have a p orbital on an atom adjacent to a double bond*:**

   1) The *p* orbital may have a single electron as in the **allyl radical** (CH_2=$CHCH_2$•).

   2) The *p* orbital may be vacant as in the **allyl cation** (CH_2=$CHCH_2^+$).

   3) The *p* orbital may contain a pair of electrons as in the **allyl anion** (CH_2=$CHCH_2$**:**$^-$).

   4) It may be the *p* orbital of another double bond as in **1,3-butadiene** (CH_2=CH–CH=CH_2).

2. **Conjugated unsaturated systems:** systems that have a *p* orbital on an atom adjacent to a double bond —— molecules with delocalized π bonds.

3. **Conjugation** gives these systems special properties:

   1) Conjugated radicals, ions, or molecules are more stable than nonconjugated ones.

   2) Conjugated molecules absorb energy in the ultraviolet and visible regions of the electromagnetic spectrum.

   3) Conjugation allows molecules to undergo unusual reactions.

13.2 ALLYLIC SUBSTITUTION AND THE ALLYL RADICAL

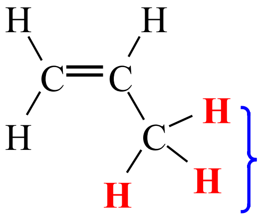
1. Addition of halogen to the double bond takes place when propene reacts with bromine or chlorine at low temperatures.

$$\underset{\textbf{Propene}}{H_2C{=}CH{-}CH_3} + \color{red}{X_2} \xrightarrow[\substack{CCl_4 \\ \text{(addition reaction)}}]{\text{low temperature}} H_2\underset{\color{red}{X}}{C}{-}\underset{\color{red}{X}}{C}H{-}CH_3$$

2. Substitution occurs when propene reacts with bromine or chlorine at very high temperatures or under very low halogen concentration.

$$\underset{\textbf{Propene}}{H_2C{=}CH{-}CH_3} + \color{red}{X_2} \xrightarrow[\substack{\text{or low conc. of } X_2 \\ \text{(substitution reaction)}}]{\text{high temperature}} H_2C{=}CH{-}CH_2\color{red}{X} + H\color{red}{X}$$

3. **Allylic substitution:** any reaction in which an **allylic hydrogen atom** is replaced.


Allylic hydrogen atoms

13.2A ALLYLIC CHLORINATION (HIGH TEMPERATURE)

1. Propene undergoes allylic chlorination when propene and chlorine react in the gas phase at 400°C —— the "**Shell Process**".

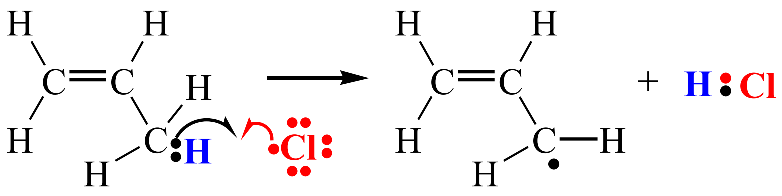
$$\underset{\textbf{Propene}}{H_2C{=}CH{-}CH_3} + \color{red}{Cl_2} \xrightarrow[\text{gas phase}]{400\ ^{o}C} \underset{\substack{\textbf{3-Chloropropene} \\ \textbf{(allyl chloride)}}}{H_2C{=}CH{-}CH_2\color{red}{Cl}} + H\color{red}{Cl}$$

2. The mechanism for allylic substitution:

1) ***Chain-initiating Step***

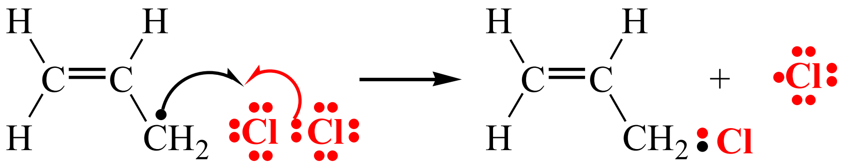
$$:\ddot{\underset{..}{Cl}}:\ddot{\underset{..}{Cl}}: \xrightarrow{h\nu} 2\ \cdot\ddot{\underset{..}{Cl}}:$$

2) ***First Chain-propagating Step***



Allyl radical

3) ***Second Chain-propagating Step***



Allyl chloride

3. Bond dissociation energies of C–H bonds:

CH_2=$CHCH_2$—H **Propene**	⟶	**CH_2=$CHCH_2$• + H•** **Allyl radical**	$\Delta H°$ = **360** kJ mol^{-1}
$(CH_3)_3$C—H **Isobutane**	⟶	**$(CH_3)_3$C• + H•** **3° Radical**	$\Delta H°$ = **380** kJ mol^{-1}
$(CH_3)_2$CH—H **Propane**	⟶	**$(CH_3)_2$CH• + H•** **2° Radical**	$\Delta H°$ = **395** kJ mol^{-1}
$CH_3CH_2CH_2$—H **Propane**	⟶	**$CH_3CH_2CH_2$• + H•** **1° Radical**	$\Delta H°$ = **410** kJ mol^{-1}
CH_2=CH—H **Ethene**	⟶	**CH_2=CH• + H•** **Vinyl radical**	$\Delta H°$ = **452** kJ mol^{-1}

1) An allylic C–H bond of propene is broken with greater ease than even the 3° C–H bond of isobutene and with far greater ease than a vinylic C–H bond.

H_2C=CH—CH_2—**H** + •X: ⟶ H_2C=CH—CH_2• + **H:X**   ***E*****$_{act}$ is low**

H_3C—CH=CH—**H** + •X: ⟶ H_3C—CH=CH• + **H:X**   ***E*****$_{act}$ is high**

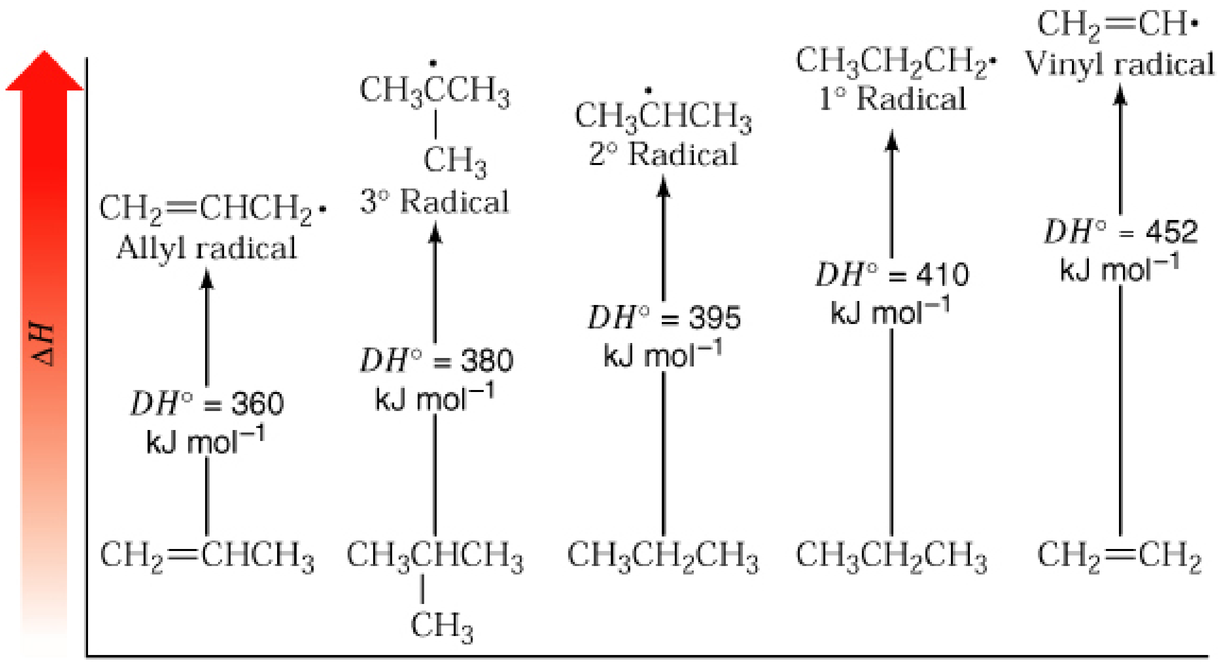


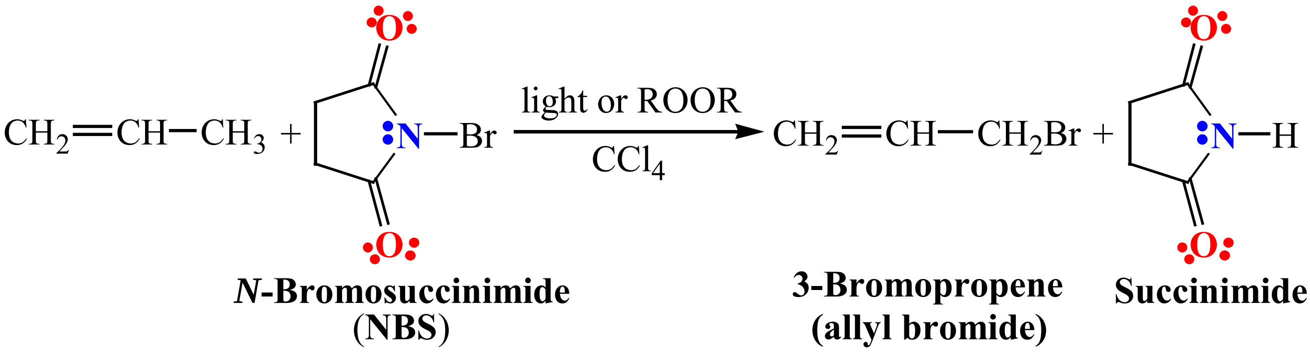
Figure 13.1 **The relative stability of the allyl radical compared to 1°, 2°, 3°, and vinyl radicals. (The stabilities of the radicals are relative to the hydrocarbon from which was formed, and the overall order of stability is allyl > 3° > 2° > 1° > vinyl).**

2) Relative stability of radicals:

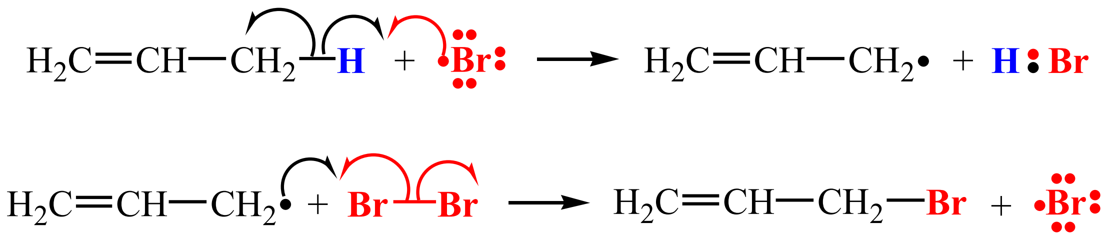
allylic or allyl > 3° > 2° > 1° > vinyl or vinylic

13.2B Allylic Bromination with *N*-Bromosuccinimide (Low Concentration of Br_2)

1. Propene undergoes allylic bromination when treated with *N*-bromosuccinimide (NBS) in CCl_4 in the presence of peroxides or light.

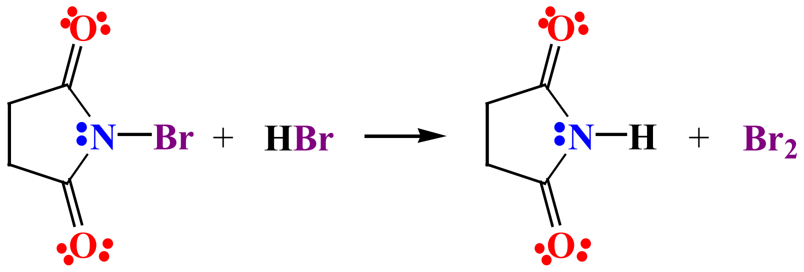


1) The reaction is initiated by the formation of a small amount of Br•.
2) The main propagation steps:



3) NBS is nearly insoluble in CCl_4 and provides a constant but very low concentration of bromine in the reaction mixture.

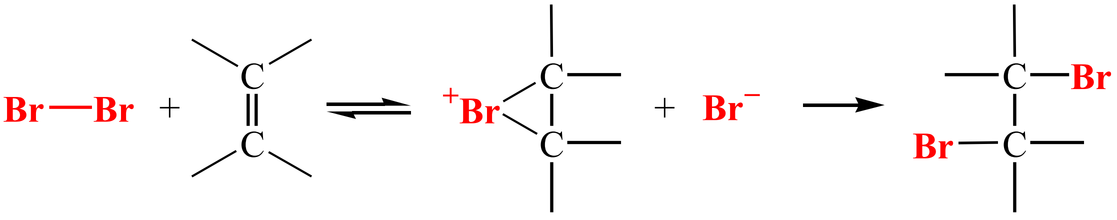
   i) NBS reacts very rapidly with the HBr formed in the substitution reaction ⇒ each molecule of HBr is replaced by one molecule of Br_2.



   ii) ***In a nonpolar solvent and with a very low concentration of bromine, very little bromine adds to the double bond***; it reacts by substitution and replaces an allylic hydrogen atom.

2. **Why does a low concentration of bromine favor allylic substitution over addition?**

1) The mechanism for addition of Br_2 to a double bond:



   i) In the first step only one atom of the bromine molecule becomes attached to the alkene ***in a reversible step***.

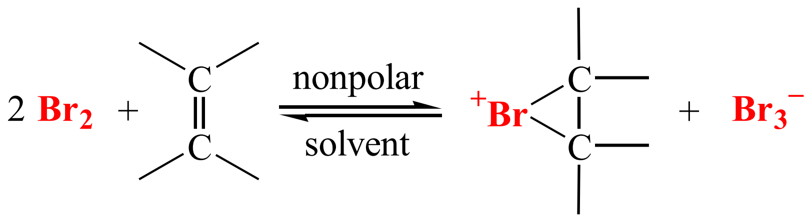
   ii) The other atom (now the bromide ion) becomes attached in the second step.

   iii) If the concentration of bromine is low, the equilibrium for the first step will lie far to the left. Even when the bromonium ion forms, the probability of its

finding a bromide ion in its vicinity is low. ⇒ These two factors slow the addition so that allylic substitution competes successfully.

2. **The use of a nonpolar solvent slows addition.**

1) There are no polar solvent molecules to solvate (and thus stabilize) the bromide ion formed in the first step, the bromide ion uses a bromine molecule as a substitute. ⇒ In a nonpolar solvent the rate equation is second order with respect to bromine.



$$\text{rate} = k\left[\text{>C=C<}\right][Br_2]^2$$

i) The low bromine concentration has a more pronounced effect in slowing the rate of addition.

3. **Why a high temperature favors allylic substitution over addition?**

1) The addition reaction has **a substantial negative entropy change** ⇒ At low temperatures, the $T\Delta S°$ term in $\Delta G° = \Delta H° - T\Delta S°$, **is not large enough to offset** the favorable $\Delta H°$ term.

2) At high temperatures, the $T\Delta S°$ term becomes more significant, $\Delta G°$ becomes more positive ⇒ the equilibrium becomes more unfavorable.

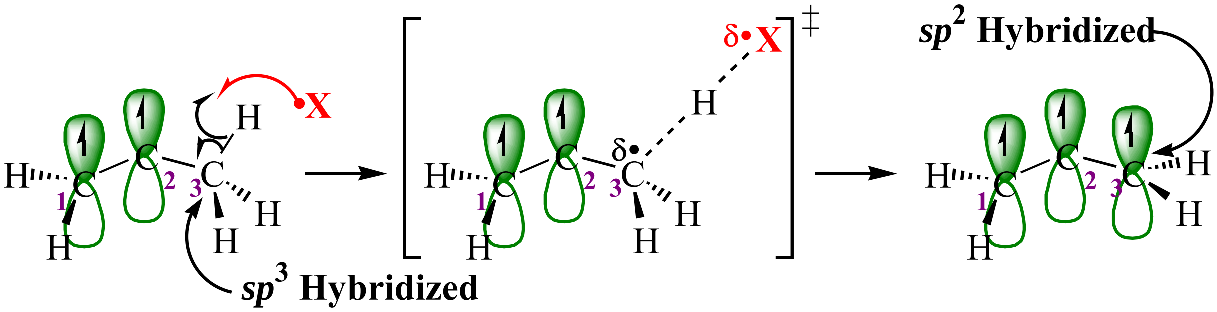
13.3 The Stability of the Allyl Radical

13.3A Molecular Orbital Description of the Allyl Radical

1. As the allylic hydrogen atom is abstracted from propene, the sp^3-hybridized carbon atom of the methyl group changes its hybridization state to sp^2.

1) The p orbital of this new sp^2-hybridized carbon atom overlaps with the p orbital of the central carbon atom ⇒ in the allyl radical three p orbitals overlap to form a set of π MOs that encompass all three carbon atoms.

2) The new p orbital of the allyl radical is ***conjugated*** with those of the double bond ⇒ the allyl radical is a ***conjugated unsaturated system***.



3) The unpaired electron of the allyl radical and the two electrons of the π bond are **delocalized** over all three carbon atoms.

i) This delocalization of the unpaired electron accounts for the greater stability of the allyl radical when compared to 1°, 2°, and 3° radicals.

ii) Although some delocalization occurs in 1°, 2°, and 3° radicals, delocalization is not as effective because it occurs through σ bonds.

6-11-02

2. Formation of three π MOs of the allyl radical:

1) The bonding π MO is of lowest energy ⇒ it encompasses all three carbon atoms and is occupied by two spin-paired electrons.

i) The bonding π orbital is the result of having p orbitals with lobes of the same sign overlap between adjacent carbon atoms ⇒ increases the π electron density in the regions between the atoms.

2) The nonbonding π orbital is occupied by one unpaired electron, and it has a node at the central carbon atom ⇒ the unpaired electron is located in the vicinity of carbon 1 and 3 only.

3) The antibonding π MO results when orbital lobes of opposite sign overlap between adjacent carbon atoms ⇒ there is a node between each pair of carbon atoms.

i) The antibonding orbital of the allyl radical is of highest energy and is empty in the ground state of the radical.

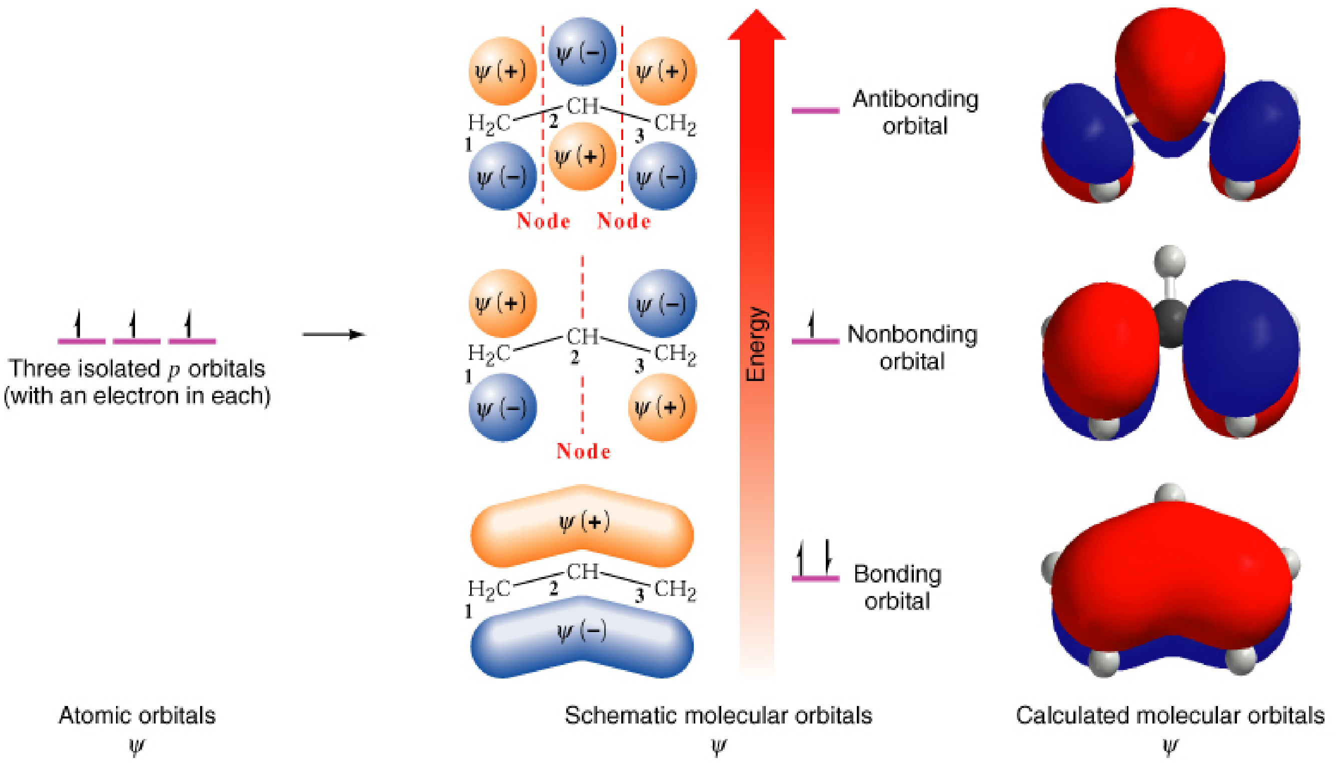
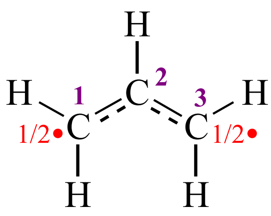


Figure 13.2 **Combination of three atomic *p* orbitals to form three π molecular orbitals in the allyl radical. The bonding π molecular orbital is formed by the combination of the three *p* orbitals with lobes of the same sign overlapping above and below the plane of the atoms. The nonbonding π molecular orbital has a node at C2. The antibonding π molecular orbital has two nodes: between C1 and C2, and between C2 and C3. The shapes of molecular orbitals for the allyl radical calculated using quantum mechanical principles are shown alongside the schematic orbitals.**

3. The structure of allyl radical given by MO theory:



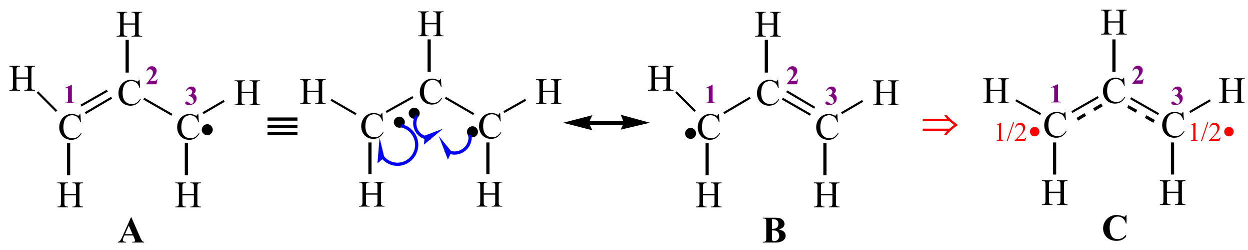
1) The dashed lines indicate that both C–C bonds are partial double bonds ⇒ ***there is a π bond encompassing all three atoms***.

i) The symbol 1/2• besides the C1 and C3 atoms ⇒ ***the unpaired electron spends***

its time in the vicinity of C1 and C3 ⇒ the two ends of allyl radical are ***equivalent***.

13.3B Resonance Description of the Allyl Radical

1. Resonance structures of the allyl radical:



1) **Only the electrons are moved but not the atomic nuclei**.

i) In resonance theory, when two structures can be written for a chemical entity **that differ only in the positions of the electrons**, the entity can not be represented by either structure alone but is a ***hybrid*** of both.

ii) Structure **C** blends the features of both resonance structures **A** and **B**.

iii) The resonance theory gives the same structure of the allyl radical as in the MO approach ⇒ the C–C bonds of the allyl radical are partial double bonds and the unpaired electron is associated only with C1 and C3 atoms.

iv) Resonance structures **A** and **B** are equivalent ⇒ *C1 and C3 are equivalent*.

2) The resonance structure shown below is **not a proper resonance structure** because resonance theory dictates that ***all resonance structures must have the same number of unpaired electrons***.

i) This structure indicates that an unpaired electron is associated with C2.

$\bullet CH_2-\dot{C}H-CH_2\bullet$ (**an incorrect resonance structure**)

2. In resonance theory, ***when equivalent structures can be written for a chemical species, the chemical species is much more stable than any resonance structure (when taken alone) would indicate***.

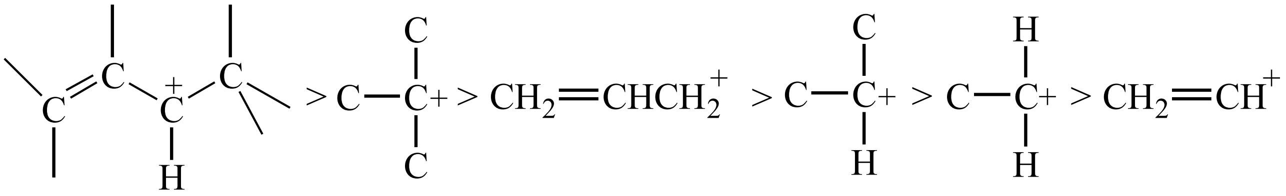
1) Either **A** or **B** alone resembles a 1° radical.

2) Since **A** and **B** are ***equivalent resonance structures***, the allyl radical should be much more stable than either, that is, much more stable than a 1° radical ⇒ **the allyl radical is even more stable than a 3° radical**.

13.4 THE ALLYL CATION

1. The allyl cation ($CH_2{=}CHCH_2^+$) is an unusually stable carbocation ⇒ **it is more stable than a 2° carbocation and is almost as stable as a 3° carbocation**.

1) **The relative order of carbocation stability:**



Substituted allylic > 3° > Allyl > 2° > 1° > Vinyl

1. **MO description** of the allyl cation:

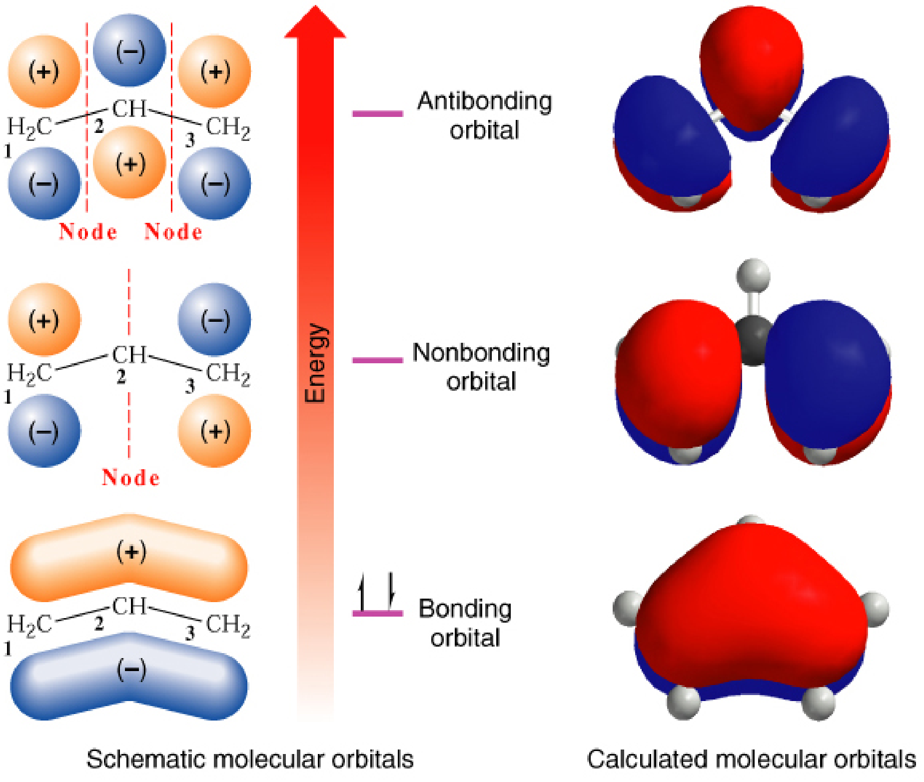


Figure 13.3 **The π molecular orbitals of the allyl cation. The allyl cation, like the allyl radical, is a conjugated unsaturated system. The shapes of molecular orbitals for the allyl cation calculated using quantum mechanical principles are shown alongside the schematic orbitals.**

1) The bonding π molecular orbital of the allyl cation contains two spin-paired electrons.
2) The nonbonding π molecular orbital of the allyl cation is empty.
3) Removal of an electron from an allyl radical gives the allyl cation ⇒ the electron is removed from the nonbonding π molecular orbital.

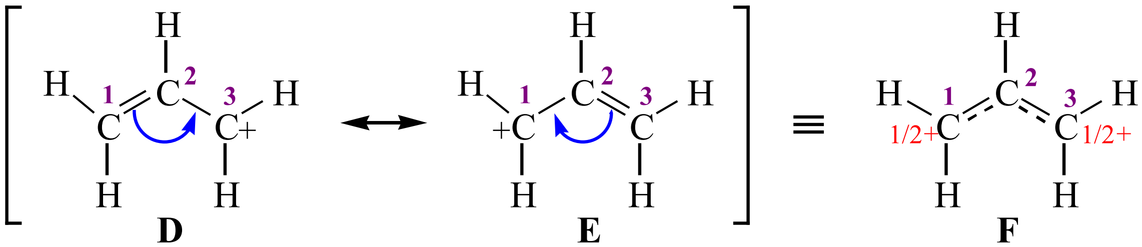
$$CH_2{=}CHCH_2\bullet \longrightarrow CH_2{=}CHCH_2^+$$

i) Removal of an electron from a nonbonding orbital requires less energy than removal of an electron from a bonding orbital.

ii) The positive charge on the allyl cation is ***effectively delocalized*** between C1 and C3.

iii) **The ease of removal of a nonbonding electron** and **the delocalization of charge** account for the **unusual stability** of the allyl cation in MO theory.

2. **Resonance theory** depicts the allyl cation as a hybrid of structures **D** and **E**:



D **E** **F**

1) **D** and **E** are ***equivalent*** resonance structures ⇒ the allyl cation should be unusually stable.
2) The positive charge is located on C3 in **D** and on C1 in **E** ⇒ the positive charge is ***delocalized*** over both carbon atoms and C2 carries none of the positive charge.
3) The hybrid structure **F** includes charge and bond features of both **D** and **E**.

13.5 SUMMARY OF RULES FOR RESONANCE

13.5A RULES FOR WRITING RESONANCE STRUCTURES

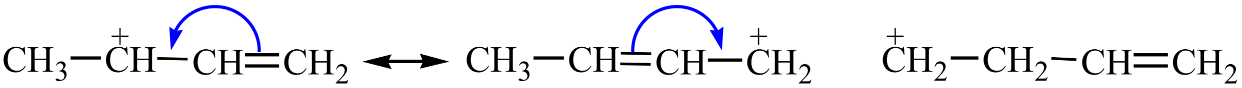
1. Resonance structures exist only on paper.

1) Resonance structures are useful because they allow us to describe molecules, radicals, and ions for which a single Lewis structure is inadequate.

2) Resonance structures or resonance contributors are connected by double-headed arrows (↔) ⇒ the real molecule, radical, or ion is a hybrid of all of them.

2. In writing resonance structures, only electrons are allowed to be moved.

1) The positions of the nuclei of the atoms must remain the same in all of the structures.



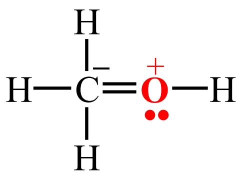
1 **2** **3**

These are resonance structures for the allylic cation formed when 1,3-butadiene accepts a prooton.

This is not a proper resonance structure for the allylic cation because a hydrogen atom has been moved.

2) Only the electrons of π bonds and those of lone pairs are moved.

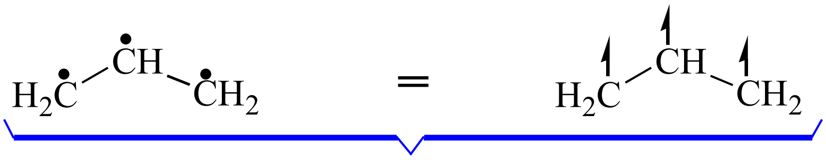
3. All of the structures must be proper Lewis structures.



This not a proper resonance structure for methanol because carbon has five bonds.

Elements of the first major row of the periodic table cannot have more than eight electrons in their valence.

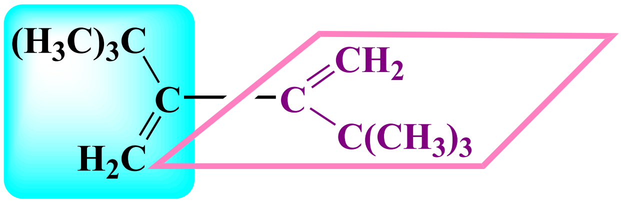
4. All structures must have the same number of unpaired electrons.



This is not a proper resonance structure for the allyl radical because it does not contain the same number of unpaired electrons as CH_2=$CHCH_2$•.

5. **All atoms that are a part of the delocalized system must be in a plane or be nearly planar.**

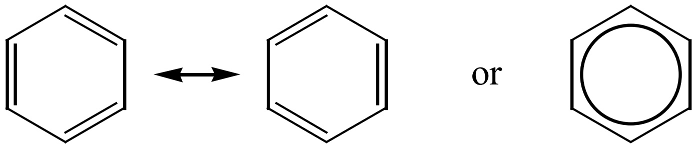
1) 2,3-Di-*tert*-butyl-1,3-butadiene behaves like a ***nonconjugated*** dienes because the bulky *tert*-butyl groups twist the structure and prevent the double bonds from lying in the same plane ⇒ the *p* orbitals at C2 and C3 do not overlap and delocalization (and therefore resonance) is prevented.



6. **The energy of the actual molecule is lower than the energy that might be estimated for any contributing structure.**

1) Structures **4** and **5** resembles 1° carbocations and yet the allyl cation is more stable than a 2° carbocation ⇒ ***resonance stabilization***.

$$\underset{\mathbf{4}}{CH_2{=}CH{-}\overset{+}{C}H_2} \longleftrightarrow \underset{\mathbf{5}}{\overset{+}{C}H_2{-}CH{=}CH_2}$$



Resonance structures for benzene **Representation of hybrid**

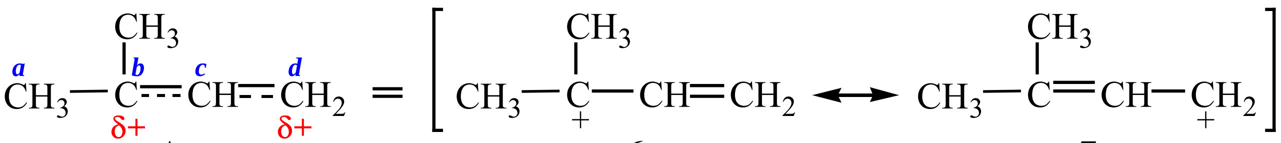
7. **Equivalent resonance structures make equal contributions to the hybrid, and a system described by them has a large resonance stabilization.**

8. **For nonequivalent resonance structures, the more stable a structure is the greater is its contribution to the hybrid.**

1) Structures that are not equivalent do not make equal contributions.

2) Cation **A** is a hybrid of structures **6** and **7**.

i) Structure **6** makes greater contribution than **7** because **6** is a more stable 3° carbocation while **7** is a 1° cation.



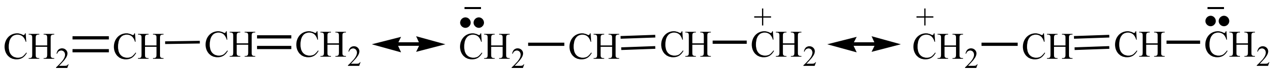
A **6** **7**

ii) Structure **6** makes greater contribution means that the partial positive charge on carbon ***b*** of the hybrid will be larger than the partial positive charge on carbon ***d***.

iii) It also means that the bond between carbon atoms ***c*** and ***d*** will be more like a double bond than the bond between carbon atoms ***b*** and ***c***.

13.5B Estimating the Relative Stability of Resonance Structures

1. The more covalent bonds a structure has, the more stable it is.



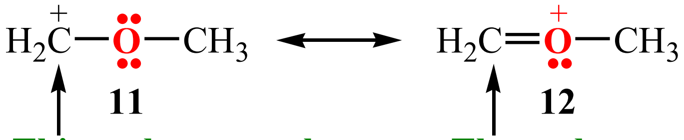
8 **9** **10**

This is structure is the most stable because it contains more covalent bonds.

2. Structures in which all of the atoms have a complete valence shell of electrons are especially stable and make large contributions to the hybrid.

1) Structure **12** makes a larger stabilizing contribution to the cation below than **11** because all of the atoms of **12** have a complete valence shell.

i) **12** has more covalent bonds than **11**.



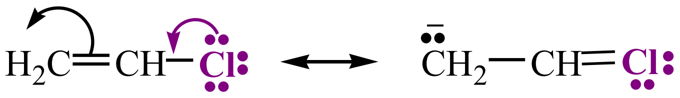
11 **12**

This carbon atom has only six electrons. **The carbon atom has eight electrons.**

3. Charge separation decreases stability.

1) Separating opposite charges requires energy.

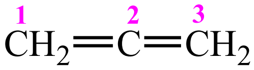
i) Structures in which opposite charges are separated have greater energy than those that have no charge separation.



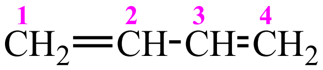
13 **14**

13.6 ALKADIENES AND POLYUNSATURATED HYDROCARBONS

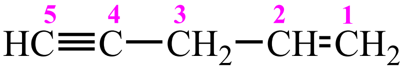
1. **Alkadiene** and **alkatriene** ⇒ **diene** and **triene**; **alkadiyne** and **alkenyne** ⇒ **diyne** and **enyne**.



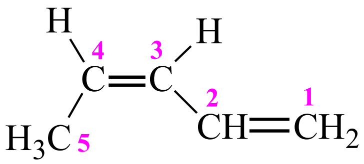
1,2-Propadiene (allene)



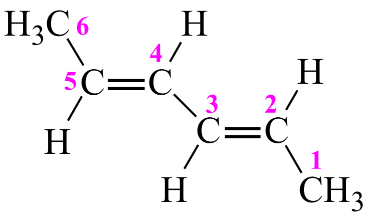
1,3-Butadiene



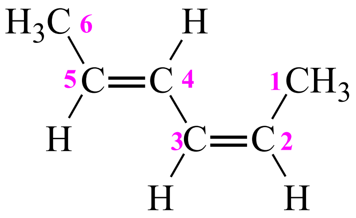
1-Penten-4-yne



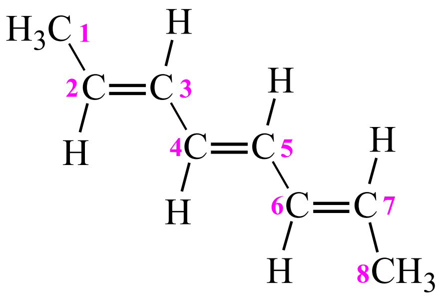
(3*Z*)-1,3-Pentadiene
(*cis*-1,3-pentadiene)



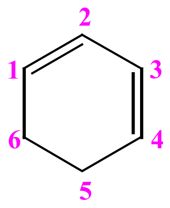
(2*E*,4*E*)-2,4-Hexadiene
(*trans*,*trans*-2,4-hexadiene)



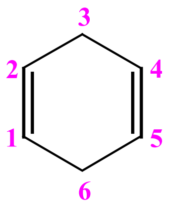
(2*Z*,4*E*)-2,4-Hexadiene
(*cis*,*trans*-2,4-hexadiene)



(2*E*,4*E*,6*E*)-2,4,6-Octatriene
(*trans*,*trans*,*trans*-2,4,6-octatriene)



1,3-Cyclohexadiene



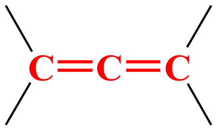
1,4-Cyclohexadiene

2. The multiple bonds of polyunsaturated compounds are classified as being **cumulated**, **conjugated**, or **isolated**.
   1) The double bonds of allene are said to be cumulated because one carbon (the central carbon) participates in two double bonds.
      i) Hydrocarbons whose molecules have cumulated double bonds are called **cumulenes**.

ii) The name **allene** is used as a class name for molecules with two cumulated double bonds.

CH_2=C=CH_2

Allene



A cumulated diene

iii) Appropriately substituted allenes give rise to chiral molecules.

iv) Cumulated dienes have had some commercial importance, and cumulated double bonds are occasionally found in naturally occurring molecules.

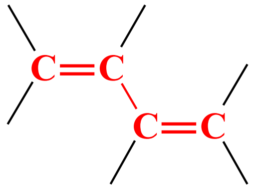
vi) In general, cumulated dienes are less stable than isolated dienes.

2) An example of a **conjugated** diene is 1,3-butadiene.

i) In conjugated polyenes the double and single bonds ***alternate*** along the chain.

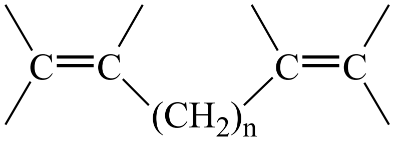
CH_2=CH—CH=CH_2

1,3-Butadiene



A cconjugated diene

3) If one or more saturated carbon atoms intervene between the double bonds of an alkadiene, the double bonds are said to be ***isolated***.



An isolated diene (n ≠ 0)

CH_2=CH—CH_2—CH=CH_2

1,4-Pentadiene

i) The double bonds of isolated double dienes undergo all of the reactions of alkenes.

13.7 1,3-Butadiene: Electron Delocalization

13.7A Bond Length of 1,3-Butadiene

1. The bond length of 1,3-butadiene:

$\overset{1}{C}H_2 = \overset{2}{C}H — \overset{3}{C}H = \overset{4}{C}H_2$

1.34 Å 1.47 Å 1.34 Å

1) The C1—C2 bond and the C3—C4 bond are (within experimental error) the same length as the C–C double bond of ethene.
2) The central bond of 1,3-butadiene (1.47 Å) is considerably shorter than the single bond of ethane (1.54 Å).
   i) All of the carbon atoms of 1,3-butadiene are sp^2 hybridized ⇒ the central bond results from overlapping sp^2 orbitals.
   ii) A σ bond that is sp^3-sp^3 is ***longer*** ⇒ the central bond results from overlapping sp^2 orbitals.

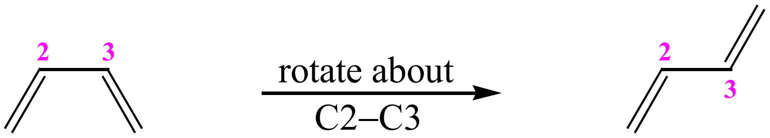
3) There is a steady decrease in bond length of C–C single bonds as the hybridization state of the bonded atoms changes from sp^3 to sp.

Table13.1 Carbon-Carbon Single Bond Lengths and Hybridization State

Compound	Hybridization State	Bond Length (Å)
$H_3C—CH_3$	sp^3-sp^3	1.54
$H_2C=CH—CH_3$	Sp^2-sp^3	1.50
$H_2C=CH—CH=CH_2$	Sp^2-sp^2	1.47
$HC≡C—CH_3$	sp-sp^3	1.46
$HC≡C—CH=CH_2$	sp-sp^2	1.43
$HC≡C—C≡CH$	sp-sp	1.37

13.7B CONFORMATIONS OF 1,3-BUTADIENE

1. There are two possible planar conformations of 1,3-butadiene:
   the s-cis and the s-trans conformations.



s-cis Conformation of 1,3-butadiene s-trans Conformation of 1,3-butadiene

1) The s-trans conformation of 1,3-butadiene is the predominant one at room temperature.

13.7C MOLECULAR ORBITALS OF 1,3-BUTADIENE

1. The central carbon atoms of 1,3-butadiene are close enough for overlap to occur between the *p* orbitals of C2 and C3.

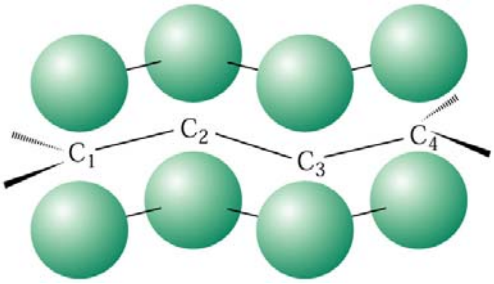


Figure 13.4 The *p* orbitals of 1,3-butadiene, stylized as spheres. (See Figure 13.5 for the shapes of calculated molecular orbitals for 1,3-butadiene.)

1) This overlap is not as great as that between the orbitals of C1 and C2.
2) The C2–C3 overlap gives the central bond partial double bond character and allows the four π electrons of 1,3-butadiene to be delocalized over all four atoms.

2. The π molecular orbitals of 1,3-butadiene:
   1) Two of the π molecular orbitals of 1,3-butadiene are bonding molecular orbitals.
      i) In the ground state these orbitals hold the four π electrons with two spin-paired electrons in each.
   2) The other two π molecular orbitals are antibonding molecular orbitals.
      i) In the ground state these orbitals are unoccupied.
   3) An electron can be excited from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) when 1,3-butadiene absorbs light with wavelength of 217 nm.

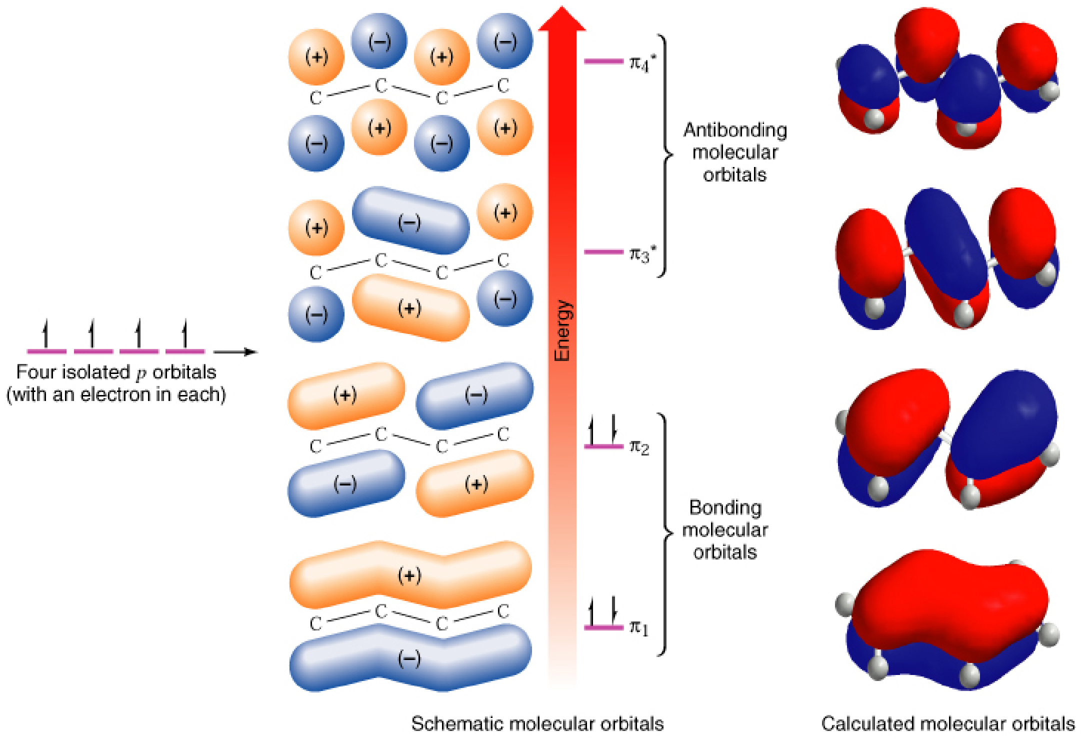


Figure 13.5 **Formation of the π molecular orbitals of 1,3-butadiene from four isolated *p* orbitals. The shapes of molecular orbitals for 1,3-butadiene calculated using quantum mechanical principles are shown alongside the schematic orbitals.**

13.8 The Stability of Conjugated Dienes

1. Conjugated alkadienes are thermodynamically more stable than isolated alksdienes.

Table13.2 **Heats of Hydrogenation of Alkenes and Alkadienes**

Compound	H_2 (mol)	$\Delta H°$ (kJ mol^{-1})
1-Butene	1	–127
1-Pentene	1	–126
trans-2-Pentene	1	–115
1,3-Butadiene	2	–239
trans-1,3-Pentadiene	2	–226
1,4-Pentadiene	2	–254
1,5-Hexadiene	2	–253

2. Comparison of the heat of hydrogenation of 1,3-butadiene and 1-butene:

			$\Delta H°$ (kJ mol^{-1})
$2\ CH_2{=}CHCH_2CH_3 + 2\ H_2 \longrightarrow 2\ CH_3CH_2CH_2CH_3$		(2×-127)	$= -254$
1-Butene			
$CH_2{=}CHCH{=}CH_2 + 2\ H_2 \longrightarrow 2\ CH_3CH_2CH_2CH_3$			$= \underline{-239}$
1,3-Butadiene		Difference	15 kJ mol^{-1}

1) Hydrogenation of 1,3-butadiene liberates 15 kJ mol^{-1} ***less*** than expected ⇒ **conjugation imparts some extra stability to the conjugated system**.

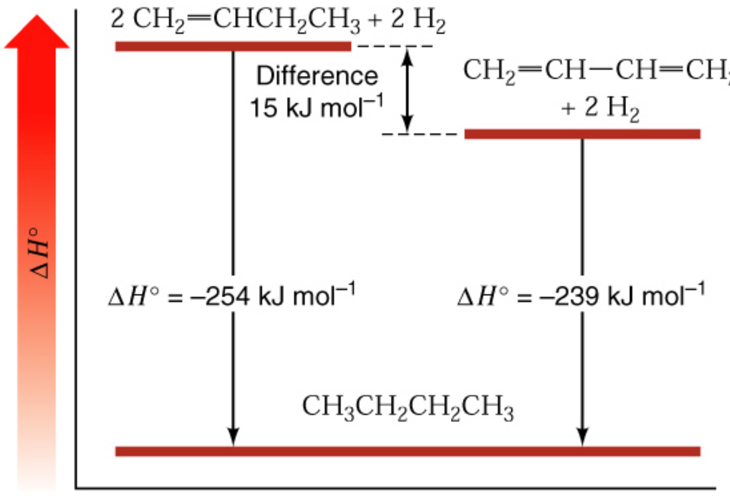
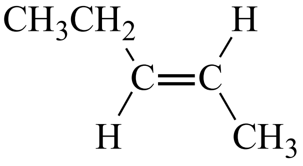


Figure 13.6 **Heats of hydrogenation of 2 mol of 1-butene and 1 mol of 1,3-butadiene.**

3. Assessment of the conjugation stabilization of *trans*-1,3-pentadiene:

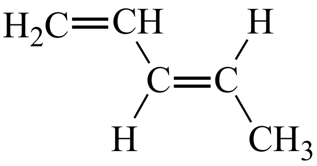
$CH_2{=}CHCH_2CH_3$

1-Pentene $\qquad \Delta H° = -126$ kJ mol^{-1}



***trans*-2-Pentene** $\qquad \underline{\Delta H° = -115 \text{ kJ mol}^{-1}}$

Sum $= -241$ kJ mol^{-1}



***trans*-1,3-Pentadiene** $\qquad \underline{\Delta H° = -226 \text{ kJ mol}^{-1}}$

Diffference $= -15$ kJ mol^{-1}

1) Conjugation affords *trans*-1,3-pentadiene an extra stability of 15 kJ mol^{-1} ⇒ ***conjugated dienes are more stable than isolated dienes***.

4. What is the source of the extra stability associated with conjugated dienes?.

1) In part from the stronger central bond that they contain (sp^2-sp^2 C–C bond).

2) In part from the additional delocalization of the π electrons that occurs in conjugated dienes.

13.9 ULTRAVIOLET-VISIBLE SPECTROSCOPY

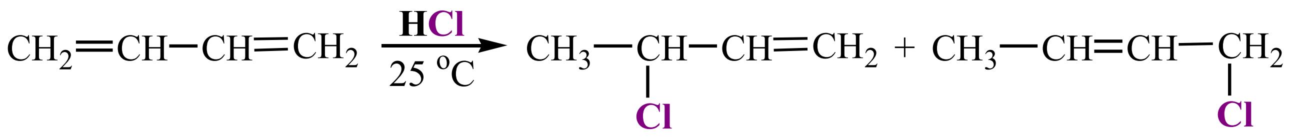
13.9A UV-VIS SPECTROPHOTOMERS

13.9B ABSORPTION MAXIMA FOR NONCONJUGATED AND CONJUGATED DIENES

13.9C ANALYTICAL USES OF UV-VIS SPECTROSCOPY

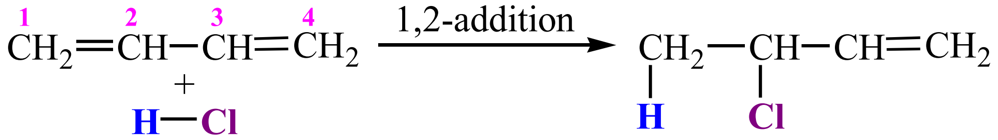
13.10 ELECTROPHILIC ATTACK ON CONJUGATED DIENES: 1,4-ADDITION

1. 1,3-butadiene reacts with one molar equivalent of HCl to produce two products: 3-chloro-1-butene and 1-chloro-2-butene.



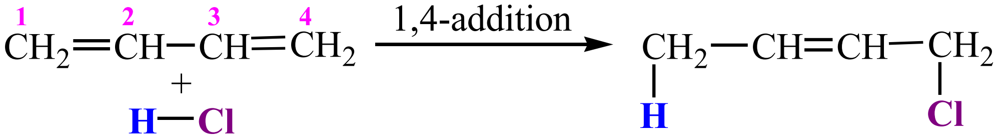
1,3-Butadiene **3-Chloro-1-butene** **1-Chloro-2-butene**

1) **1,2-Addition:**



3-Chloro-1-butene

2) **1,4-Addition:**

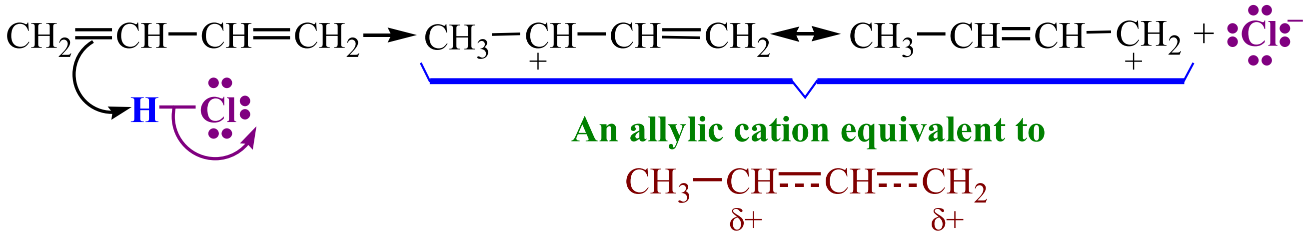


1-Chloro-2-butene

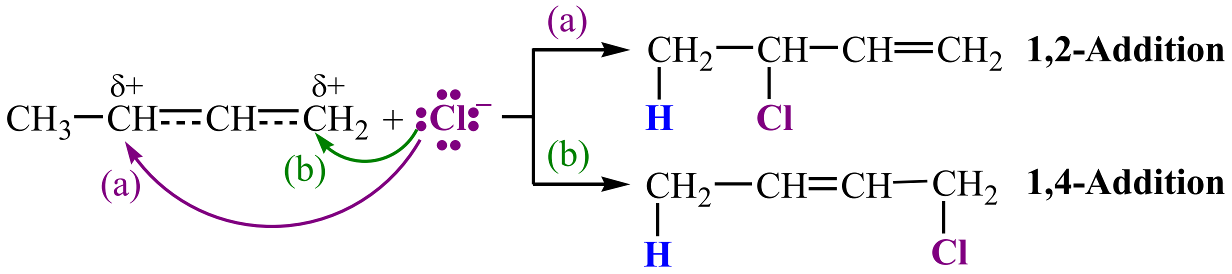
2. 1,4-Addition can be attributed directly to the stability and delocalized nature of allylic cation.

 1) The mechanism for the addition of HCl:

Step 1

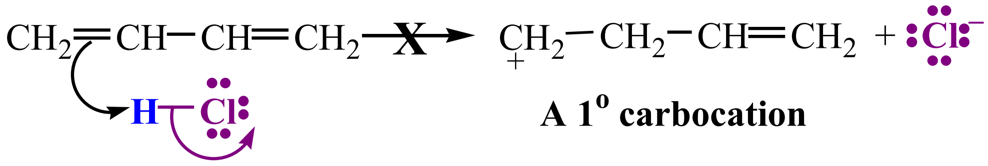


Step 2



 2) In step 1, a proton adds to one of the terminal carbon atoms of 1,3-butadiene to form the more stable carbocation ⇒ a resonance stabilized allylic cation.

  i) Addition to one of the inner carbon atoms would have produced a much less 1° cation, one that could not be stabilized by resonance.



3. 1,3-Butadiene shows 1,4-addition reactions with electrophilic reagents other than HCl.

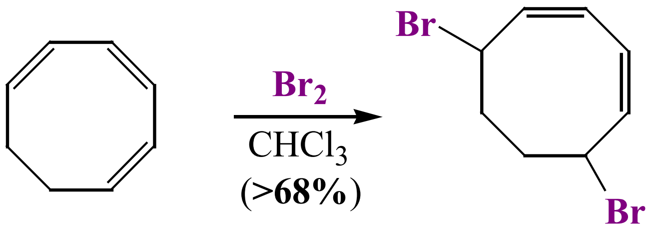
$$CH_2{=}CHCH{=}CH_2 \xrightarrow[40^{o}C]{\textbf{HBr}} CH_3CH\textbf{Br}CH{=}CH_2 + CH_3CH{=}CHCH_2\textbf{Br}$$

(20%) (80%)

$$CH_2{=}CHCH{=}CH_2 \xrightarrow[-15^{o}C]{\textbf{Br}_2} CH_2\textbf{Br}CH\textbf{Br}CH{=}CH_2 + CH_2\textbf{Br}CH{=}CHCH_2\textbf{Br}$$

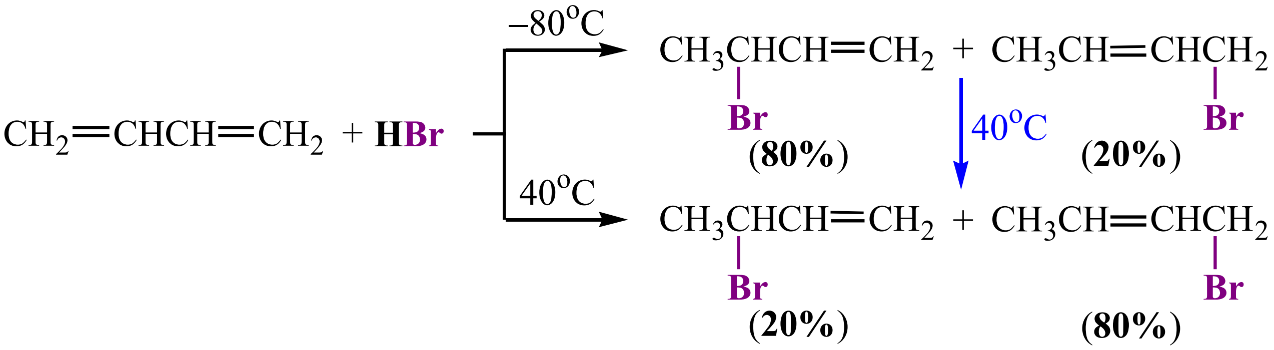
(54%) (46%)

4. Reactions of this type are quite general with other conjugated dienes.
   1) Conjugated trienes often show 1,6-addition.

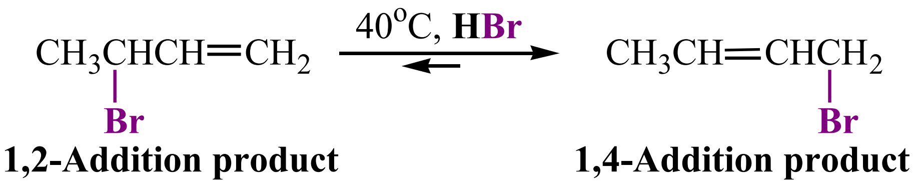


13.10A KINETIC CONTROL VERSUS THERMODYNAMIC CONTROL OF A CHEMICAL REACTION

1. The relative amounts of 1,2- and 1,4-addition products obtained from the addition of HBr to 1,3-butadiene are dependent on the reaction temperature.
   1) When 1,3-butadiene and HBr react at a low temperature (–80 °C) in the absence of peroxides, the major reaction is 1,2-addition ⇒ 80% of the 1,2-product and only 20% of the 1,4-product.
   2) At higher temperature (40 °C) the result is reversed: the major reaction is 1,4-addition ⇒ 80% of the 1,4-product and only about 20% of the 1,2-product.
   3) When the mixture formed at the lower temperature is brought to higher temperature, the relative amounts of the two products change.
      i) This new reaction mixture eventually contains the same proportion of products given by the reaction carried out at the higher temperature.



ii) At the higher temperature and in the presence of HBr, the 1,2-adduct rearranges to 1,4-product and that an equilibrium exists between them.



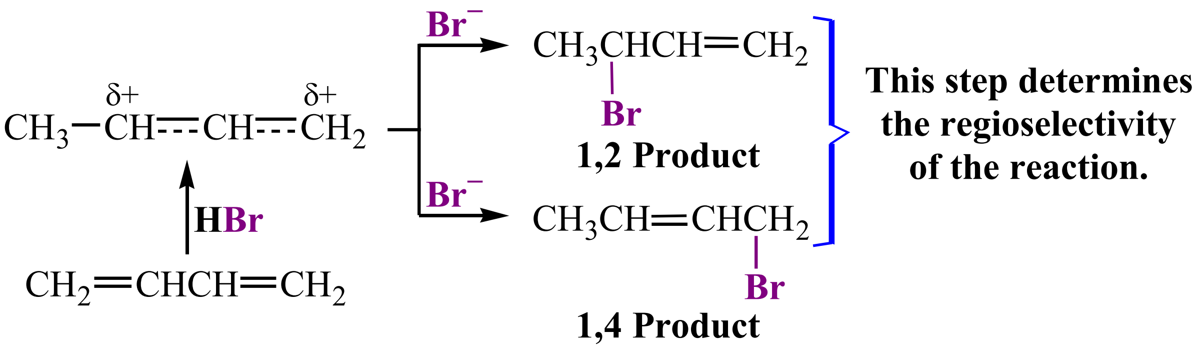
iii) The equilibrium favors the 1,4-addition product ⇒ ***1,4-adduct must be more stable***.

2. The outcome of a chemical reaction can be determined by relative rates of competing reactions and by relative stabilities of the final products.

1) At lower temperature, the relative amounts of the products of the addition are determined by the relative rates at which the two additions occur; 1,2-addition occurs faster so the 1,2-addition product is the major product.

2) At higher temperature, the relative amounts of the products of the addition are determined by the position of an equilibrium; 1,4-addition product is the more stable, so it is the major product.

3) The step that determines the overall outcome of the reaction is the step in which the bybrid allylic cation combines with a bromide ion:



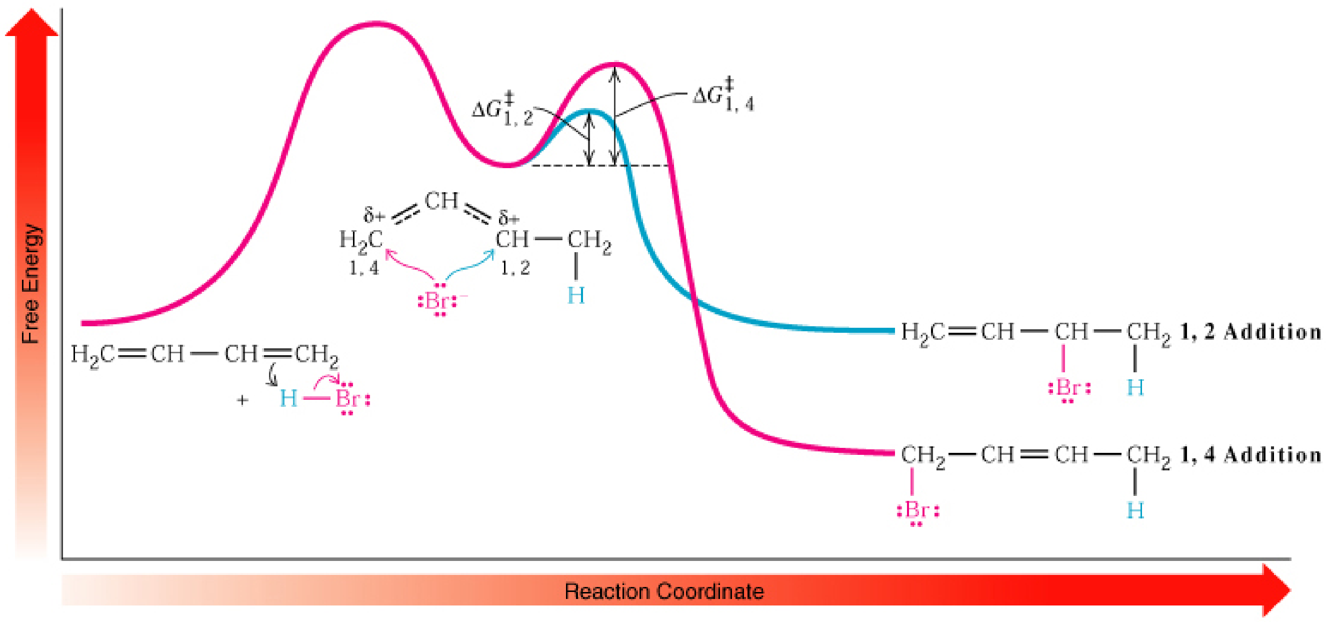


Figure 13.10 A schematic free-energy versus reaction coordinate diagram for the 1,2 and 1,4 addition of hbr to 1,3-butadiene. An allylic carbocation is common to both pathways. The energy barrier for attack of bromide on the allylic cation to form the 1,2-addition product is less than that to form the 1,4-addition product. The 1,2-addition product is kinetically favored. The 1,4-addition product is more stable, and so it is the thermodynamically favored product.

Special Topic A

CHAIN-GROWTH POLYMERS

A.1 INTRODUCTION

A.1A POLYMER AGE

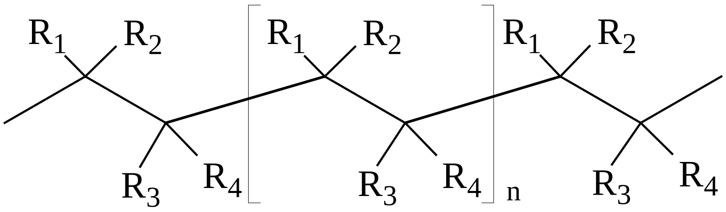
1. 石器時代 ⇒ 陶器時代 ⇒ 銅器時代 ⇒ 鐵器時代 ⇒ 聚合物時代
   1) The development of the processes by which synthetic polymers are made was responsible for the remarkable growth of the chemical industry in the twentieth century.
   2) Although most of the polymeric objects are combustible, incineration is not always a feasible method of disposal because of attendant air pollution ⇒ "**Biodegradable plastics**".

聚合物材料與結構材料比較表

	伸張強度 [1]	單位重量伸張強度 [1]
鋁合金	1.0	1.0
鋼(延伸)	5.0	1.7
Kevlar®	5.4	10.0
聚乙烯	5.8	15.0

1. 相對於鋁合金
2. Kevlar®: 聚對苯二甲醯對二胺基苯

一些簡單的聚合物 —— 顯示聚合物可配合各種需求



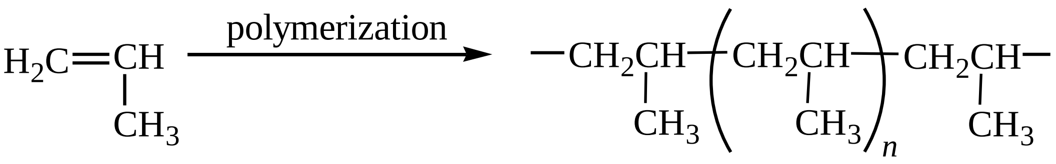
R^1, R^2, R^3, R^4	名稱	產品	1982 年美國產量
H, H, H, H	聚乙烯 (Polyethylene)	塑膠袋；瓶子；玩具	5,700,000 公噸
F, F, F, F	聚四氟乙烯 (Teflon) (Polytetrafluoroethylene)	廚具；絕緣	
H, H, H, CH_3	聚丙烯 (Polypropylene)	地毯(室內、室外)；瓶子	1,600,000 公噸
H, H, H, Cl	聚氯乙烯 (Polyvinylchloride)	塑膠膜；唱片；水電管	2,430,000 公噸
H, H, H, C_6H_5	聚苯乙烯 (Polystyrene)	絕緣 (隔熱)；傢俱；包裝材料	2,326,000 公噸
H, H, H, CN	聚丙烯氰 (Polyacrylonitrile)	毛線；編織物；假髮	920,000 公噸
H, H, H, $OCOCH_3$	聚乙酸乙烯酯 (Polyvinyl acetate)	黏著劑；塗料；磁碟片	500,000 公噸
H, H, Cl, Cl	聚二氯乙烯 (Polyvinylidine chloride)	食物包裝材料 (如 Saran®)	
H, H, CH_3, $COOCH_3$	聚甲基丙烯酸甲酯 (Polymethyl methacrylate)	玻璃替代物；保齡球；塗料	

A.1B NATURALLY OCCURRING POLYMERS

1. **Proteins** — silk, wool.
2. **Carbohydrates (polysaccharides)** — starches, cellulose of cotton and wood.

A.1C CHAIN-GROWTH POLYMERS

1. Polypropylene is an example of chain-growth polymers (addition polymers):

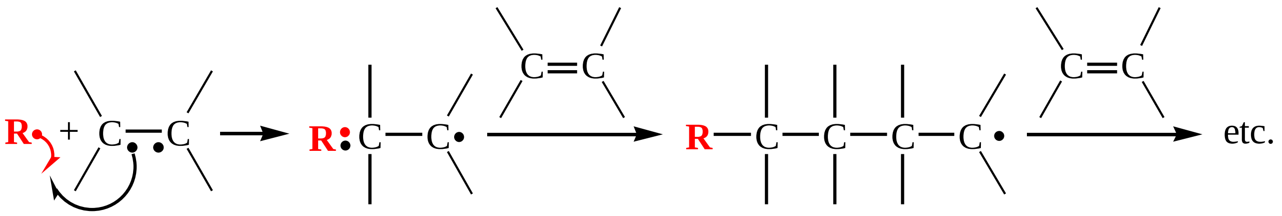


Propylene **Polypropylene**

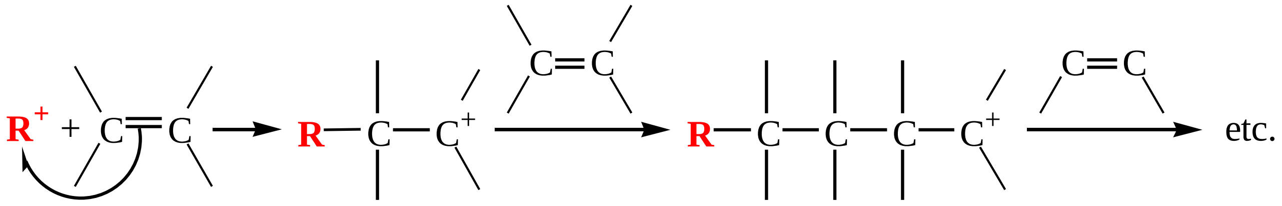
A.1D MECHANISM OF POLYMERIZATION

1. The addition reactions occur through **radical**, **cationic**, or **anionic** mechanisms:

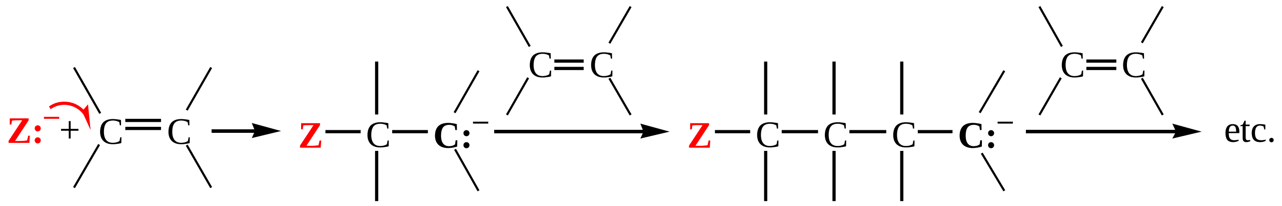
   1) ***Radical Polymerization***



   2) ***Cationic Polymerization***

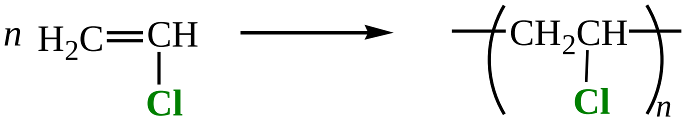


   3) ***Anionic Polymerization***



A.1E RADICAL POLYMERIZATION

1. Poly(vinyl chloride) (**PVC**):

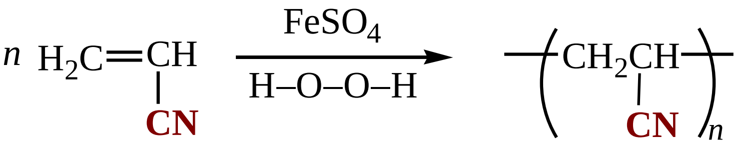


Vinyl chloride **Poly(vinyl chloride) (PVC)**

1) PVC has a molecular weight of about 1,500,000 and is a hard, brittle, and rigid.
2) PVC is used to make pipes, rods, and compact discs.
3) PVC can be softened by mixing it with esters (called ***plasticizers***).
   i) The softened material is used for making “vinyl leather”, plastic raincoats, shower curtains, and garden hoses.

4) Exposure to vinyl chloride has been linked to the development of a rare cancer of the liver called angiocarcinoma [angiotensin: 血管緊張素、血管緊張；carcinoma: 癌] (first noted in 1974 and 1975 among workers in vinyl chloride factories).
   i) Standards have been set to limit workerrs’ exposure to less than one part per million (ppm) average over an 8-h day.
   ii) The US Food and Drug Administration (FDA) has banned the use of PVC in packing materials for food.

2. Polyacrylonitrile (**Orlon**):

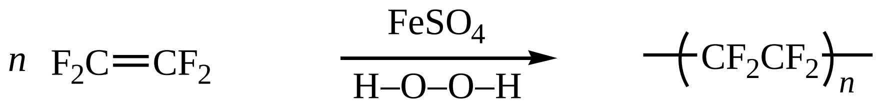


Acrylonitrile **Polyacrylonitrile (Orlon)**

1) Polyacrylonitrile decomposes before it melts ⇒ melt spinning cannot be used for the production of fibers.

2) Polyacrylonitrile is soluble in *N*,*N*-dimethylformamide (DMF) ⇒ the solution can be used to spin fibers.
3) Polyacrylonitrile fibers are used in making carpets and clothing.

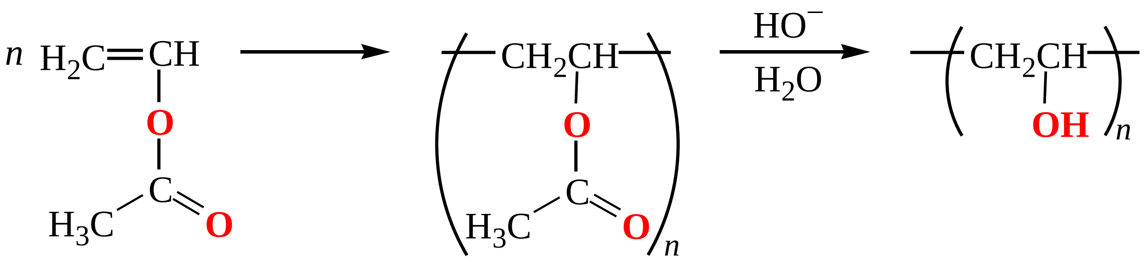
3. Polytetrafluoroethylene (**Teflon**, PTFE):



Tetrafluoroethylene **Polyetrafluoroethylene (Teflon)**

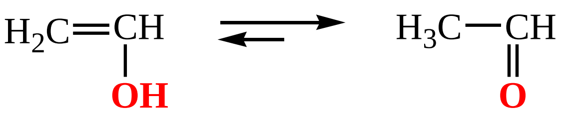
1) Teflon is made by polymerizing tetrafluoroethylene in aqueous suspension.
2) The reaction is highly exothermic ⇒ water helps to dissipate the heat that is produced.
3) Teflon has a melting point (327 °C) that is unusually high for an addition polymer.
4) Teflon is highly resistant to chemical attack and has a low coefficient of friction ⇒ Teflon is used in greaseless bearings, in liners for pots and pans, and in many special situations that require a substance that is highly resistant to corrosive chemicals.

4. Poly(vinyl alcohol):



Vinyl acetate **Poly(vinyl acetate)** **Polyvinyl alcohol**

1) Vinyl alcohol is an unstable compound that tautomerizes spontaneously to acetaldehyde.



Vinyl alcohol **Acetaldehyde**

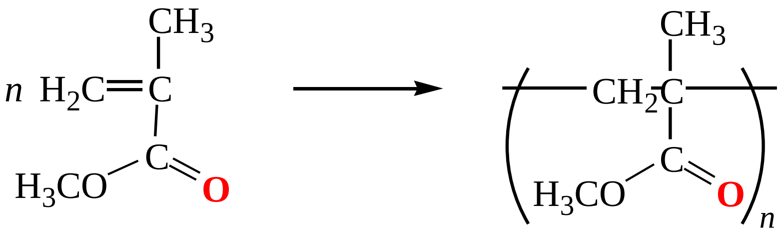
i) Poly(vinyl alcohol), a water-soluble polymer, cannot be made directly ⇒ polymerization of vinyl acetate to poly(vinyl acetate) followed by hydrolysis to poly(vinyl alcohol).

ii) The hydrolysis is rarely carried to completion because the presence of a few ester groups helps confer water solubility of the product.

iii) The ester groups apparently helps keep the polymer chain apart, and this permits hydration of the hydroxyl groups.

2) Poly(vinyl alcohol) in which 10% of the ester groups remain dissolves readily in water.
3) Poly(vinyl alcohol) is used to manufacture water-soluble films and adhesives.
4) Poly(vinyl acetate) is used as an emulsion in water-based paints.

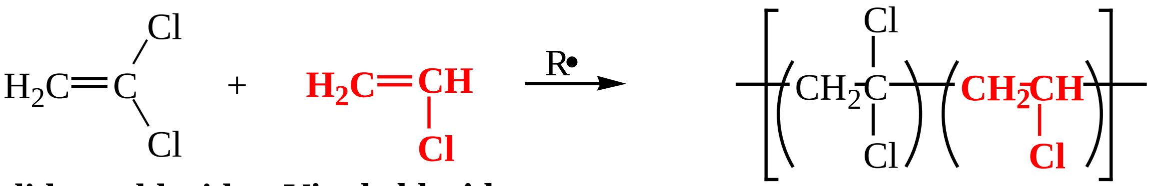
5. Poly(methyl methacrylate):



Methyl methacrylate **Poly(methyl methacrylate)**

1) Poly(methyl methacrylate) has excellent optical properties and is marketed under the names Lucite, Plexiglas, and Perspex.

6. Copolymer of vinyl chloride and vinylidene chloride:



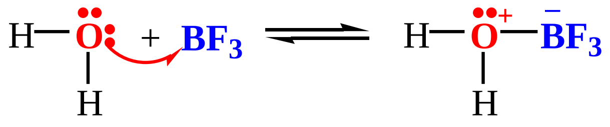
Vinylidene chloride (excess) **Vinyl chloride** **Saran Wrap**

1) *Saran Wrap* used in food packing is made by polymerizing a mixture in which the vinylidene chloride predominates.

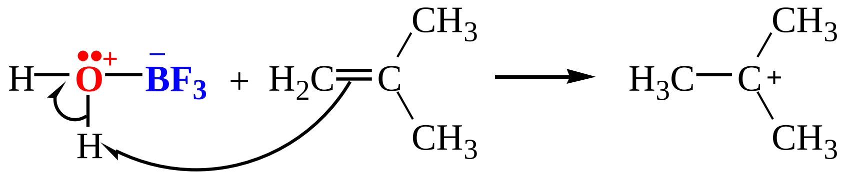
A.1F CATIONIC POLYMERIZATION

1. Alkenes polymerize when they are treated with strong acids:

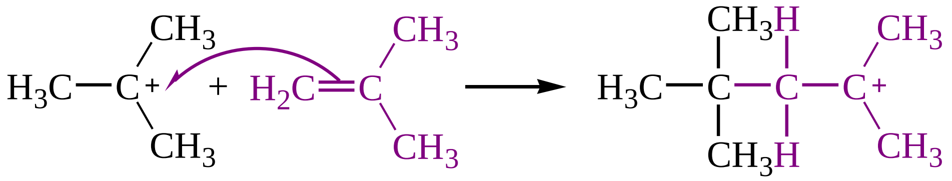
Step 1



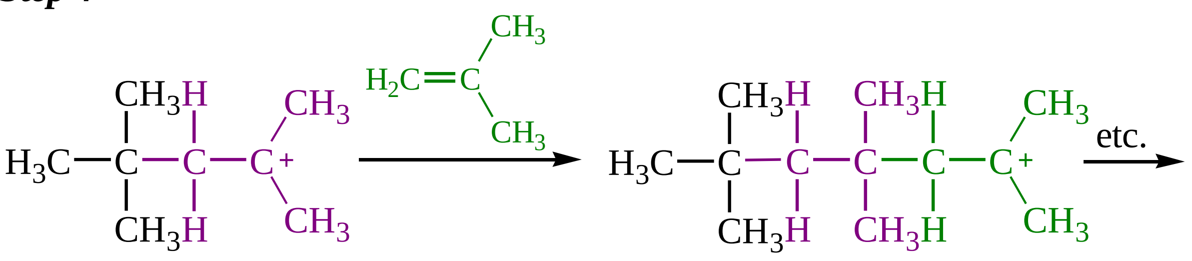
Step 2



Step 3



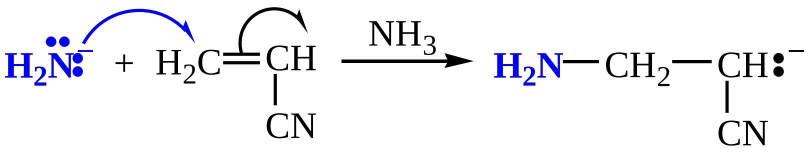
Step 4

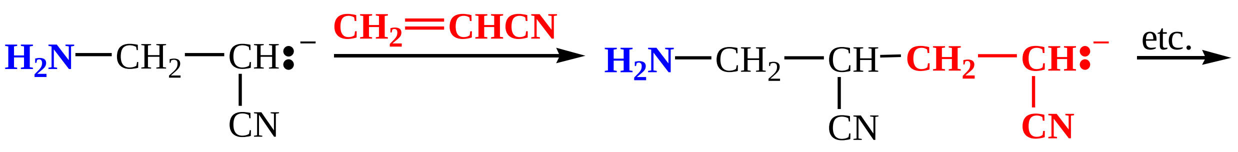


1) The catalysts used for cationic polymerizations are usually Lewis acids that contain a small amount of water.

A.1G ANIONIC POLYMERIZATION

1. Alkenes containing electron-withdrawing groups polymerize in the presence of strong bases:

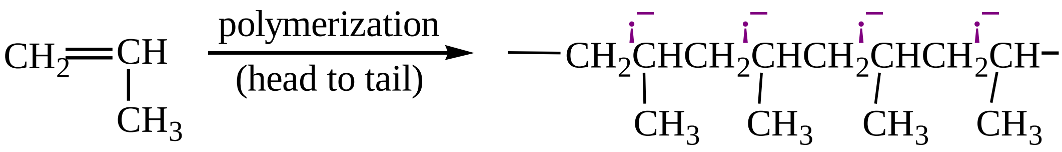




1) Anionic polymerization of acrylonitrile is less important in commercial production than the radical process.

A.2 STEREOCHEMISTRY OF CHAIN-GROWTH POLYMERIZATION

1. Head-to-tail polymerization of propylene produces a polymer in which every other atom is a stereocenter.
2. Many of the physical properties of propylene produced in this way depend on the stereochemistry of these stereocenters.



A.2A ATACTIC POLYMERS

1. The stereochemistry at the stereocenters is random, the polymer is said to be **atactic** (***a***, without + Greek: ***taktikos***, order).

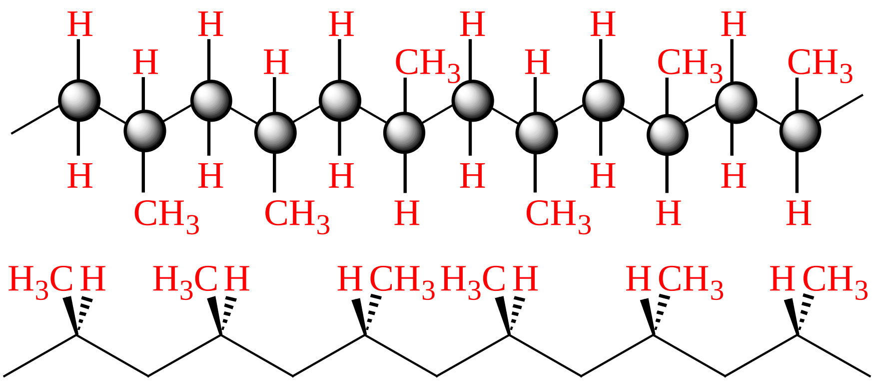


Figure 10.1 **Atactic polypropylene. (In this illustration a "stretched" carbon chain is used for clarity.**

1) In atactic polypropylene the methyl groups are randomly disposed on either side of the stretched carbon chain ⇒ (*R*-*S*) designations along the chain is random.
2) Polypropylene produced by radical polymerization at high pressure is atactic.
3) Atactic polymer is noncrystalline ⇒ it has a low softening point and has poor mechanical properties.

A.2B SYNDIOTACTIC POLYMERS

1. The stereochemistry at the stereocenters alternates regularly from one side of the stretched chain to the other is said to be **syndiotactic** (*syndio*: two together) ⇒ (*R*-*S*) designations along the chain would alternate (*R*), (*S*), (*R*), (*S*), (*R*), (*S*) and ao on.

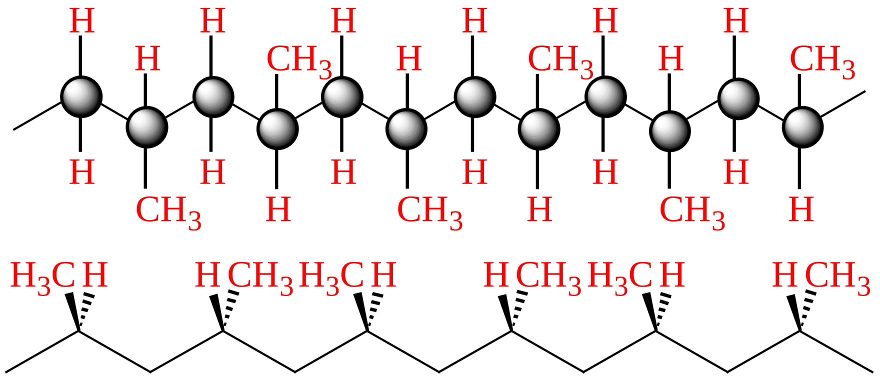


Figure 10.2 Syndiotactic polypropylene.

A.2C ISOTACTIC POLYMERS

1. The stereochemistry at the stereocenters is all on one side of the stretched chain is said to be **isotactic** (*iso*: same).

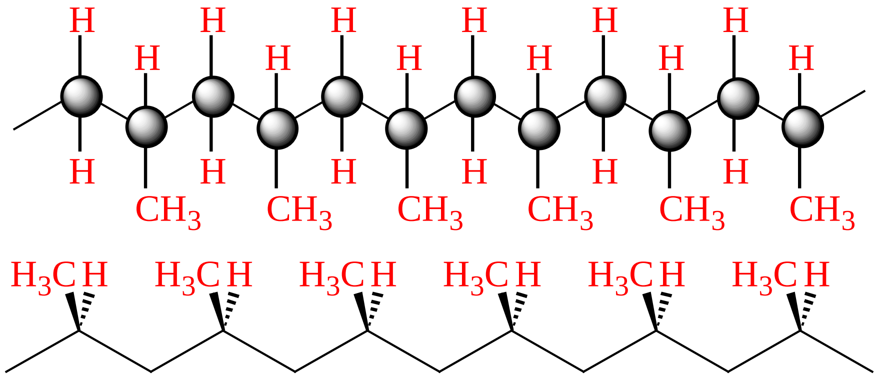


Figure 10.3 Isotactic polypropylene.

1) The configuration of the stereocenters are either all (*R*) or all (*S*) depending on which end of the chain is assigned higher preference.

A.2D ZIEGLER-NATTA CATALYSTS

1. Karl Ziegler (a German chemist) and Giulio Natta (an Italian chemist) announced

independently in 1953 the discovery of catalysts that permit stereochemical control of polymerization reactions ⇒ **they were awarded the Nobel Prize in Chemistry for their discoveries in 1963**.

1) The Ziegler-Natta catalysts are prepared from transition metal halides and a reducing agent ⇒ the catalysts most commonly used are prepared from titanium tetrachloride ($TiCl_4$) and a trialkylaluminum (R_3Al).

2. Ziegler-Natta catalysts are generally employed as suspended solids ⇒ polymerization probably occurs at metal atoms on the surfaces of the particles.

1) The mechanism for the polymerization is an ionic mechanism.

2) There is evidence that polymerization occurs through an insertion of the alkene monomer between the metal and the growing polymer chain.

3. Both syndiotactic and isotactic polypropylene have been made using Ziegler-Natta catalysts.

1) The polymerizations occur at much lower pressures, and the polymers that are produced are much higher melting than atactic polypropylene.

i) Isotactic polypropylenemelts at 175 °C.

4. Syndiotactic and isotactic polymers are much more crystalline than atactic polymers.

1) The regular arrangement of groups along the chains allows them to fit together better in a crystal structure.

i) Isotactic polypropylenemelts at 175 °C.

5. Atactic poly(methyl methacrylate) is a noncrystalline glass.

1) Syndiotactic and isotactic poly(methyl methacrylate) are crystalline and melt at 160 and 200 °C, respectively.